MEDICAL GRAND ROUNDS

THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL SCHOOL

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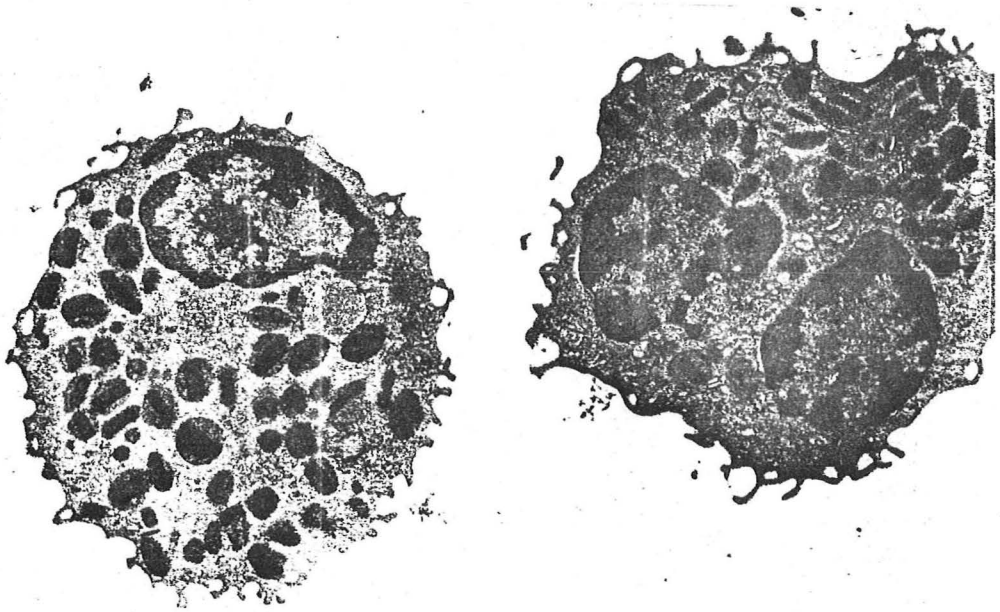
THE EOSINOPHIL LEUCOCYTE:
A Cell in Search of a Role



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The eosinophil leucocyte was first distinguished by its coarse granules by Jones in 1846 and intensive study of the cell was initiated in 1879 when Ehrlich described its striking affinity for acid-aniline dyes such as eosin, the quality which has given the cell its name. Since that time, this cell, whose individuality glistens in stained preparations, has attracted much attention by students of the leucocytes, yet it is one of the few remaining cells for which no special function can be stated. The eosinophil occurs in all vertebrates and in some insects and its appearance in the primitive latimeria suggests that it may phylogenetically precede the development of the lymphoid system (100). It is classified as a member of the polymorphonuclear leucocyte series, is produced in the bone marrow, and dwells in the bloodstream during its migration to some peripheral tissue. Although displaying certain morphological and behavioral similarities with the neutrophil leucocyte, the distinctive nature of the eosinophil is manifest in its characteristic granules as well as its different response to certain immunological situations, parasitic diseases, acute infections, endotoxins, and adrenal corticosteroids. Today's discussion will provide a brief survey of the plethora of recent research on eosinophil physiology and eosinophil behavior in intact animals and to review the available clinical observations on eosinophilia and eosinopenia. It is hoped that the observations made during the carefully controlled, although complex milieu of the research laboratory might provide some predictive and interpretive value for the clinician; conversely, a renewed interest in clinical and pathological observations of eosinophil behavior may yet suggest fundamentally new approaches of research which might eventually provide clarification of the function of this elusive cell.

MORPHOLOGY AND HISTOCHEMISTRY

The eosinophil is slightly larger than the neutrophil, being 12 to 17 μ in diameter in man. The nucleus is essentially indistinguishable from that of the neutrophil, being an annular ring in the rat and mouse (239, 260) and lobulated in man. Nuclear processes may have ceased in the mature cell, as suggested by the concentration of dense (presumably inactive) chromatin peripherally and the absence of a nucleolus (282). In contrast, the cells are well endowed with cytoplasmic organelles for metabolic activity. The mitochondria of the eosinophil are larger and more numerous than those of the neutrophil; the golgi zone, better developed; and ribosomes and small profiles of rough endoplasmic reticulum are found among numerous small vesicles of smooth endoplasmic reticulum and glycogen particles (282). These differences from the neutrophil are compatible with the more active metabolic state of the eosinophil (19, 172). There is also a definite difference in cell membrane; not visible morphologically, it is manifest by an increased resistance to changes in osmolarity in solvents such as acetone, a property which is the basis for the method of direct eosinophil counting (71, 229).

The most distinctive morphological aspect of the eosinophil is the granule. Although the size and number of eosinophil granules vary between species from 200 to 400 granules of 0.2 μ diameter in rats and mice to 25 to 50 granules of 1 μ diameter in horses (109), their development, morphology and histochemistry are remarkably similar. The immature cell contains predominantly round, homogeneous granules which do not contain crystalloids (272).

The mature eosinophil contains two types of granules. The smaller is 0.1 to 0.2 μ in diameter, round, and homogeneous on electron microscopy (210). The larger is the characteristic eosinophilic body, which is 0.4 to 0.8 μ in diameter, ovoid in shape, and contains a crystalloid core or "internum". This internum is an osmophilic oblong structure characterized by regular crystalline lines at 30 or 40 Å in rodents and man, respectively (41, 174). This is the localization of one third of the granule protein, consisting of an arginine rich basic protein of low molecular weight (6- to 12,000 daltons) (96) which is insoluble at physiological pH and binds tightly to acid-aniline dyes, probably explaining the characteristic eosinophilic staining of the cells (30).

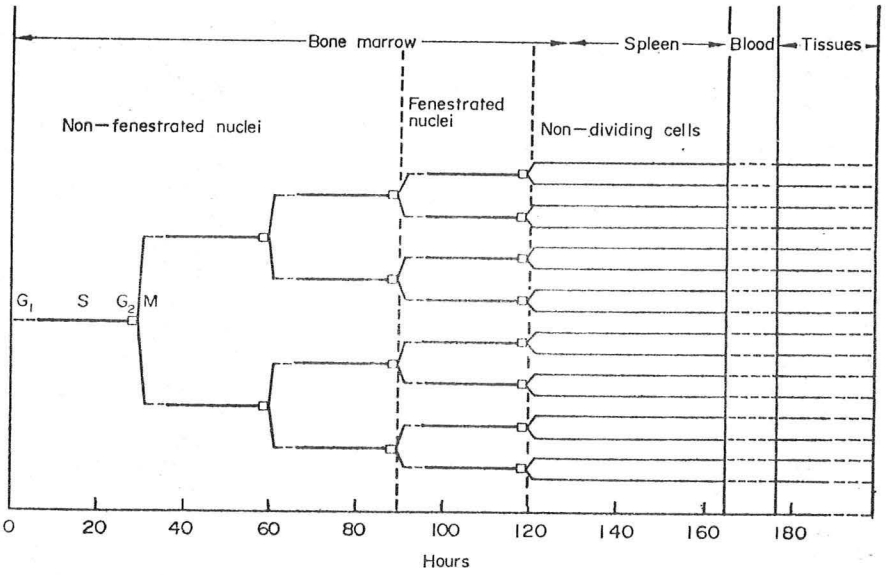
The granules of the cell contain a variety of hydrolytic enzymes including acid phosphatase, glucuronidase, cathepsin, ribonuclease, and aryl sulphatase, and a large quantity of peroxidase (5). Eosinophil peroxidase is distinctive from neutrophil peroxidase by spectral studies (10), by its resistance to cyanide (126, 66), and by the observation of a clinical syndrome with an absence of neutrophil peroxidase without abnormality of the eosinophil peroxidase (145). Other enzyme activities of eosinophil granules include both kinin production and kininase activity (the former operative at pH 7.4 and 20% oxygen and the latter at pH 7.0 and 5% oxygen) (169, 170) and plasminogen (21). Unlike neutrophil granules, eosinophil granules do not contain lysozyme or phagocytin (109).

During phagocytosis, the granules coalesce with phagosomes with membrane fusion in a manner indistinguishable from neutrophil phagocytosis (9). During phagocytosis, the internum remains intact and may be found free within the phagosome (282). This persistence of the internum may be the source of the eosinophilic needle-shaped Charcot-Leyden crystals found in secretions from tissues undergoing active eosinophilic inflammation, such as the sputum of patients with asthma (147). Although these crystals are of no known physiological significance, they remain a diagnostic aid in pointing to eosinophilic inflammation.

DEVELOPMENT AND DISTRIBUTION

Although immediately prior to birth eosinophil production may be observed in the thymus and lymph nodes (231), the vast majority are produced in the bone marrow from birth onward. The development of autoradiographic techniques for studying the kinetics of leucocyte production (53) has been followed by several studies on eosinophil production (87, 88, 42, 2, 240). Although these studies have been done in experimental animals and specific data regarding eosinophil kinetics in man are minimal, several valuable concepts arise from these animal studies which are probably qualitatively applicable to man. The eosinophil arises from an unidentified precursor and proceeds through several cell divisions before maturing and entering the bloodstream (*Fig. 1*). The stimulus for increased eosinophil production appears to act at all stages of eosinophil maturation, with a resultant shortening of all phases of the cell cycle and the provision of up to six further divisions prior to final maturation (240). In normal rats, the cell cycle time was found to be 30 hours and the total marrow transit time approximately 5.5 days. Following a stimulus to eosinophil production, the eosinophil cell cycle time was reduced to 9 hours, which would allow for 4 to 6 additional divisions, or a 16- to 64-fold increase in eosinophil production during the reduced marrow transit time of 3.6 days (240). An

FIGURE 1



Proposed pathway for eosinophil production in normal rats. Time in hours is shown on the abscissa. Doubling divisions of eosinophil precursors are shown to take place in the marrow from non-fenestrated to fenestrated forms which then mature in the spleen before entering the blood and emigrating into tissues. In normal rats sixteen progeny would be derived from each of the earliest recognizable eosinophil precursors in about 6 days. In stimulated rats, where eosinophils were shown to divide with mean cell cycle times of 9 hr, up to 1024 eosinophils could be produced from each of the earliest recognizable eosinophil precursors in the same period of time.

--From Spry, 1971 (Ref. 240)

additional implication of these observations was that alterations in eosinophil production rates could not influence blood or tissue levels of eosinophils for at least two days.

The factors controlling release of mature eosinophils from the marrow are poorly understood. The studies of Spry (241) suggest that the release of marrow eosinophils continues to follow the normal sequence of development (although more rapidly) following stimulus for eosinophilia as in the resting animal. A substance in the plasma of stimulated rats was found to induce a transient increase in the numbers of circulating eosinophils on passive transfer, but these cells could have been released from a marginated pool rather than a marrow reserve pool, as suggested by Hudson (114). After leaving the marrow, the cells apparently lodge for a period within the spleen, perhaps for further maturation, before proceeding on to their final migration into the tissues. The cells of the peripheral blood were found to be removed exponentially with a half life of 6.7 hours in rats, the same as the half life of neutrophils in normal rats, and this half life did not decrease following stimulation (241).

Following their brief residence in the circulation, eosinophils migrate into the tissues. They tend to localize in areas exposed to the external environment, such as skin, mucosa of the bronchi, gastrointestinal tract, lactating mammary glands, vagina, and wall of the uterus (202, 212). The vast majority of mature eosinophils reside within tissues, the blood-to-tissue ratio having been estimated at 1:300 to 1:500 (212, 109). The large proportion of tissue eosinophils and the assumption that it is there that they perform their function (whatever it is) have given rise to the assertion that the eosinophil should be considered a cell of the tissues, rather than the blood (116). The tissue lifespan of eosinophils is not precisely known but is probably at least a few days (109, 59). The eventual fate of the eosinophil is not well defined. A proportion of those underlying mucosal surfaces may be shed into the adjacent lumen such as the bowel (249) or bronchi, especially during conditions of local allergic inflammation (14). Many presumably degenerate at the sites of local accumulation. Some may be engulfed by macrophages (150, 234). However, definitive studies of the end of the eosinophil life cycle have been hampered by the fact that degenerative remains of many cell types will stain with eosin (100) and, conversely, the degranulation of the eosinophil (8) would result in loss of the cell's characteristic staining. Further understanding of the mechanisms of local tissue eosinophil degranulation, degeneration, and disposal could provide insight into the local function of this cell.

PHYSIOLOGY

Before considering the behavior of the eosinophil during complex immunological responses, those aspects of eosinophil behavior which have yielded to more controlled physiological study will be described.

Metabolism. Studies of eosinophil metabolism have only recently become available (57, 19, 172). These have been made on mixed populations of cells, usually peripheral blood leucocytes from patients with a transiently high eosinophilia. They rely on inference from data of mixed populations compared with a similar population devoid of eosinophils, the difference being assumed to represent the contribution of eosinophils. This also assumes that the cell populations do not interact directly (i.e., that the eosinophils present do not induce an alteration in the metabolism of the neutrophils and vice versa), an assumption which may not be correct. For examples, when eosinophils and neutrophils are mixed and exposed to chemotactic agents, depending on the specific *in vitro* model, either greater numbers of both cells are seen to migrate than when each type is tested alone (194) or the presence of eosinophils seems to markedly alter the chemotactic activity of the neutrophils present (133). Also, phagocytosis is assumed to be a physiological event, yet the hypothesis that the distinctive function of the eosinophil involves phagocytosis is uncertain. With such reservations, the following data are provided.

As with the neutrophil, the main source of energy for the eosinophil is glucose (109), and glycogen energy stores are apparent within the cytoplasm (282). Oxygen consumption by eosinophil-rich mixtures is comparable to that of pure neutrophils (19). However, the oxidation of glucose through the tricarboxylic acid cycle is higher for resting eosinophils than for neutrophils (172); this may be a manifestation of the high dehydrogenase content of eosinophils (100) or of the greater number of mitochondria present (282). Also, eosinophils are capable of a greater metabolic burst following stimulation.

Thus, eosinophils, although having a lower rate of particle phagocytosis, show greater post-phagocytic oxygen consumption (19). As in the case of the neutrophil, the eosinophil is not dependent on respiration and functions in the presence of a nitrogen atmosphere, cyanide, or dinitrophenol, whereas inhibitors of glycolysis (fluoride or iodoacetate) successfully block phagocytosis in both cell types (57). The cyanide insensitive respiratory burst is apparently operative via the hexose monophosphate shunt in the eosinophil as in the neutrophil (19, 172); however, this pathway is considerably more active in the resting eosinophil and is capable of further post-phagocytic stimulation, although the resting:stimulated ratios are less for eosinophils than for neutrophils. Equipped to function in the absence of oxygen, the cell is also apparently not affected by acidosis down to pH (57). The eosinophil therefore appears to be well designed for intense metabolic activity in adverse circumstances, such as those found in an active inflammatory site.

Motility. Eosinophils are motile and capable of migration between endothelial cells into the tissues (210) or into an area of inflammation (165) in a manner indistinguishable from that of neutrophils. Morphologically, their movement is by pseudopod formation and trailing constriction without cytoplasmic streaming. This is also the case with neutrophils (109). Their movement, however, generally appears more sluggish and less direct than that of neutrophils (105, 9).

Chemotaxis. Eosinophils congregate at the site of a variety of immunologic and inflammatory stimuli, as will be discussed. Many studies of eosinophil accumulation *in vivo* have demonstrated great diversity of possible attractants but have rarely been able to differentiate true attractants from substances which cause an immunoinflammatory response which in itself may produce the accumulation of eosinophils. Also, these *in vivo* models have demonstrated great species variability, making specific interpretation more difficult. Thus, repeated injections of a miscellany of foreign protein antigens produce a peritoneal eosinophilic exudate (37, 116, 155), yet this is accompanied by a lymphocyte-macrophage response which itself could be the source of the eosinophil attracting stimulus (193). Local intraperitoneal or intracutaneous injection of homocytotrophic antibody (similar to IgE in humans) followed by injection of antigen produces a localized anaphylactic type response associated with eosinophil accumulation (193, 194, 129). Also, eosinophils appear to congregate around stimulated mast cells (164, 192). Such observations, and the clinical association of eosinophilia with anaphylactic type allergy, prolonged the life of the hypothesis that eosinophils might be attracted by histamine. This theory was supported by the studies of R. K. Archer (13) using large doses of intracutaneous histamine in horses with the observation of a mild local accumulation of eosinophils. However, similar studies in mice (230), rats (192), guinea pigs (152, 129, 192), and in human skin window studies (83) and *in vitro* experiments (135) on human cells have failed to demonstrate any such chemotactic effect. Eosinophils are also not attracted by serotonin or bradykinin (15).

Thus, the attempt to demonstrate a selective chemotactic effect for eosinophils by the traditional vasoactive peptides of anaphylaxis has been at best controversial. The search for new substances arising from the anaphylactic tissue reaction, however, has been more successful. The perfusion of sensitized guinea pig lung (132) or human lung (131) with specific antigen was associated with release of an "eosinophil chemotactic factor of anaphylaxis"

(ECF-A). This material appears to demonstrate selective chemotactic properties for eosinophils when examined by its ability to stimulate migration through a Millipore filter in a standard Boyden chamber. This material appears to be a preformed peptide with a molecular weight of 500 to 600 daltons. ECF-A is separable from the other peptides released by mast cells, histamine, and SRS-A, and shows similar time course, divalent cation requirement, antigen dose dependence, and complement independence. The material appears to be preformed in human mast cells (171) and in human basophils (195). Thus, intact human basophils or mast cells sensitized with IgE and incubated with specific antigen in the absence of serum (hence complement independent) release a substance specifically chemotactic for eosinophils. Intraperitoneal transfer of this substance in rats was followed by a transient rise in blood and local peritoneal eosinophils, and Parrish thus suggested that such a basophil liberated substance could account for the local eosinophil accumulation which occurs during passive transfer of anaphylaxis (194, 195).

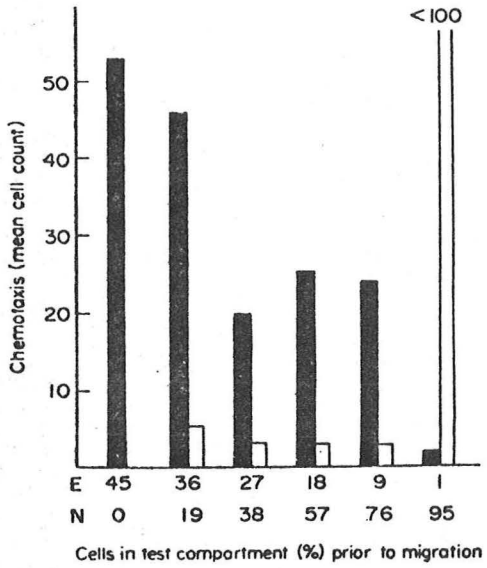
As will be noted, the eosinophil is an occasional and unpredictable accompaniment of certain malignancies. A patient with a peripheral blood eosinophilia and a large cell anaplastic tumor of the lung with local tumor eosinophilia has been described in whom the tumor was found to be producing large quantities of a material apparently identical to ECF-A (268). Such an ectopic peptide production by undifferentiated malignant cells may explain a portion of the instances of eosinophilia associated with malignancy. As will be discussed below, however, a greater number of such instances of eosinophilia may be explained by the host's immune response to the tumor or central necrosis of the tumor with associated inflammatory responses.

In addition to the observation of local peritoneal or intracutaneous eosinophilia following the induction of passive anaphylaxis, in certain circumstances local eosinophilic accumulation was found to occur following injection of preformed soluble immune complexes (193, 194). Such preformed complexes appear to be less specific and induce both a neutrophil and eosinophil accumulation at the site of injection. The eosinophil chemotactic activity of immune complexes may be partially attributed to a substance released by sensitized lymphocytes which reacts with immune complexes in the absence of complement to produce a factor specifically chemotactic for eosinophils (63). In this model, lymph node lymphocytes taken from sensitized guinea pigs were cultured in the presence or absence of specific antigen. The supernates were then incubated with species specific homologous antigen-antibody complexes in the absence of complement. This material was tested for eosinophil chemotactic properties in a standard Boyden chemotactic chamber *in vitro* and *in vivo* by injecting the supernates freed of antigen-antibody complexes intradermally into normal guinea pigs and biopsying the sites 18 hours later. Both techniques demonstrated a significant accumulation of eosinophils (63). In the guinea pig model examined, it was found that the activating complexes must be the IgG-2 (not homocytotrophic) class. Interestingly, the required antigen specificity was carrier-, not hapten-, dependent, a quality common to several activities associated with T lymphocyte processes, such as the production of migration inhibition factor and possibly the T lymphocyte "helper cell" function required for the stimulation of production of IgE (187, 188). These workers also noted that the activity of their lymphocyte-derived factor was lost if the substance was passed over a column coated with specific antibody. This prompted them to suggest that the lymphocyte product is a precursor substance (ECF_p) which contains a portion or all of the specific antigen; they postulate that the specific antigen is then cleaved by interaction with the

soluble antigen-antibody complex, thus activating the precursor substance to its functional chemotactic form (252). This is obviously a complicated system for the development of chemotactic activity and would require the activation of antibody production and persistence of antigen to form the antigen-antibody complexes and the concomitant stimulation of a lymphocyte secretory product which may arise from the T cell lymphocyte population. However, as will be discussed shortly, many of the clinical circumstances associated with eosinophilia do involve such a stimulation of multiple immunological and inflammatory mechanisms.

Further substances with eosinophil chemotactic activity may be produced by immune complexes via activation of the complement pathway. Such substances appear when fresh serum is incubated with a number of agents, also including aggregated IgG (but not IgE), endotoxin, yeast or dextran (103, 149, 135, 266, 129, 130, 142, 193). Such serum is capable of histamine liberation, passive transfer of an anaphylactic shock syndrome in guinea pigs, and chemotactic attraction of both neutrophils and eosinophils. Substances which may be active in this context are C3a, C5a, and the trimolecular complex $C\overline{567}$. Of these, the most important appears to be the split product of the 5th component of complement, C5a. This substance is capable of chemotactic attraction of both neutrophils and eosinophils in pure preparations. However, as shown in the data from Kay, Shin and Austen (133), the presence of more than 10% eosinophils in the mixture results in a greater migration of eosinophils than neutrophils.

FIGURE 2



The effect of alterations in the percentage of (■) eosinophils (E) and (□) neutrophils (N) in the test compartment on the chemotactic response to C5a derived from 40 μg of C5.

--From Kay, et al., 1973 (Ref. 133)

This is interpreted by these authors as indicating a selective competition by the eosinophils for the chemotactic agent. It should be noted that this could also be interpreted to suggest that the presence of 10% or greater eosinophils in the mixture successfully blocks the neutrophil chemotactic response to C5a.

Wissler, Stecher and Sorkin (277) have purified the active products of this complement activation and found them to be two distinct peptides. One, an anaphylatoxin, probably identical to C5a, retains the properties of histamine liberation and induction of anaphylactic shock; however, in a pure state it has no chemotactic activity. The other peptide, termed "cocytotaxin", has no apparent biological activity of its own. However, when the two are combined in varying proportions, selective chemotactic activity for either eosinophils or neutrophils (or both) is exhibited. The cells move toward the increasing anaphylatoxin gradient. The gradient of cocytotaxin has little effect. Also, the effects of cocytotaxin and its interplay with anaphylatoxin could be replaced by ATP or cyclic AMP. Therefore, the cocytotaxin appears to regulate the nature of the chemotactic effects of anaphylatoxin, rather than having any chemotactic activity of its own. Preliminary *in vivo* observations following subcutaneous injection of the purified substances were in agreement with the *in vitro* observations. It will be most interesting to see whether these complex purification procedures can be confirmed and, if so, whether the ratios of these two peptides as produced *in vivo* are dependent on the type of inflammation (or the site within the inflammation) in a manner analogous to that observed in this *in vitro* study. If such is the case, this would provide one method of explaining the observation of specific localization of cell types within varying regions of the inflammatory process.

Colley (65) has recently described the stimulation of eosinophil random migration by a substance released by lymphocytes in the absence of antibody, immune complexes or complement. Eosinophil-rich peritoneal exudate cells from mice with *Schistosoma mansoni* infection were imbedded in an agarose droplet and covered with tissue culture medium. Migration of cells from the pellet was then observed. Supernatant fluids from serum-free lymph-node cell cultures stimulated with specific antigen or phytohemagglutinin increased eosinophil migration from the pellet.

The search for substances which might induce local eosinophil accumulation by chemotaxis has been rewarding. Apparently eosinophil chemotactic agents may arise from immune stimulation of lymphocytes as in delayed hypersensitivity, homocytotropic antibody coated basophils as in anaphylactic hypersensitivity, immune complex activation of complement or immune complex activation of a lymphocyte product which might occur in situations of stimulation of multiple immune systems. Yet eosinophils partake in only a proportion of each of these types of immune responses. The very ubiquity of the chemotactic agents minimizes the possibility of obtaining insight regarding the function of the eosinophil in this varied spectrum of immune hypersensitivity states.

Phagocytosis. Since the careful studies of Weinberg and Séguin in 1915 (269) confirmed the observation of phagocytosis of bacteria by eosinophils (171), it has been repeatedly demonstrated that the eosinophils are capable of phagocytosing a wide variety of substances, including mycoplasma (285), yeast (9, 57), immune complexes (7, 9, 213, 154), denatured or aggregated (but not native) immunoglobulin (61), mast cell granules (271, 164), antibody coated red cells 269, 9), ferritin (213), and nonantigenic polystyrene particles of

between 0.09 and 0.8 μ in size (140). As with neutrophils, phagocytosis is followed by coalescence of the lysosomes by membrane fusion with the phagosome and degranulation (9). Other similarities with neutrophil phagocytosis include the metabolic response (as discussed previously) and even release of leucocyte pyrogen (172). Eosinophils do have the ability to kill ingested bacteria (19, 172), but this activity is considerably less efficient than that of neutrophils (56) and eosinophil peroxidase does not appear to take part in oxidative toxic mechanisms as occurs in neutrophil killing (47).

Studies of phagocytic activity of the eosinophil have perhaps focused attention on properties which it shares with the neutrophil, diverting attention from its distinctive characteristics. It seems unlikely that phagocytosis is the main function of this cell. Eosinophil phagocytosis of almost all particles is considerably less efficient than that of neutrophils (185, 9, 57, 19, 172). The eosinophil's greatest phagocytic ability appears to be to antigen-antibody complexes and even here neutrophils seem to perform this function more efficiently (118). Eosinophil phagocytosis is rarely observed *in vivo* (105), except in the specific condition where the cells have been previously stimulated into activity by an immunological event and then exposed to large numbers of particles for ingestion (62, 192). Eosinophils offer little or no protection against infection, even when present in great numbers, as in children with congenital neutropenia (94). As suggested by Parrish (192), phagocytosis may merely be a property retained by the eosinophil during the evolution of its special properties.

CLINICAL EOSINOPHILIA

For the purpose of this discussion, "eosinophilia" will refer to a persistent elevation of circulating eosinophils above 450 cells/mm^3. Such eosinophilia appears to be a frequent accompaniment of conditions characterized by (1) persistent or repeated exposure to large antigenic load, (2) conditions in which the antigen(s) is held in the tissues, producing a local inflammatory reaction, (3) chronic, indolent, or relapsing inflammation, and (4) especially when the antigenic and inflammatory insults occur at skin or mucosal surfaces. Although there is an immense overlap, the following classification may provide some organization to the approach to the patient with eosinophilia:

1. Allergic states
2. Infectious diseases
3. Neoplastic conditions
4. Connective tissue diseases
5. Skin diseases
6. Conditions with predominantly pulmonary symptoms and signs
7. Conditions with predominantly gastrointestinal symptoms and signs
8. Miscellaneous

Allergic states. Both local accumulation of eosinophils and occurrence of blood eosinophilia have long been recognized as part of the clinical presentation of numerous conditions with an allergic etiology, such as asthma (97), urticaria (139), anaphylaxis (178, 216), angioneurotic edema (175), and drug hypersensitivity (200). In addition to these classical allergic states, an anaphylactic-type hypersensitivity response may be involved in many of the conditions discussed below.

Infectious diseases. The dramatic and prolonged eosinophilia which accompanies parasitic infestation was first noted in ankylostomiasis in 1891 by Mueller and Reeder (182), and trichinosis in 1897 by Brown (43), and similar observations in every type of helminthic infection quickly followed. Eosinophilia may appear in a setting of essentially any metazoan infection. The appearance of eosinophilia is most uniform when the infection is invasive or migratory. Chronic eosinophilia occurs in those conditions associated with persistence of the inflammatory response (e.g., trichinosis) or continued production of new egg or larval forms (e.g., schistosomiasis) (206). Infections associated with successful encystment of the larval forms such as cysticercosis (*Taenia solium*) are typically associated with a low grade eosinophilia during the initial phases of the infection but with the eosinophil count returning to normal levels after larval encystment (72). Echinococcal disease is associated with an eosinophil count above 500/mm^3 in approximately one third of patients which is thought to be due to gradual leakage of fluid from the hydatid cyst; cyst rupture may even be associated with anaphylactic type reactions with severe associated eosinophilia (134, 127). Protozoal infections are not typically accompanied by eosinophilia during the acute infectious stage. In malaria, the typical response is a drop in the eosinophil count 24 to 36 hours before onset of an acute febrile episode, with return to the normal range thereafter (157); these patients demonstrated an infrequent occurrence of eosinophilia after therapy of the malarial process, but this may have been due to hypersensitivity to the therapeutic regimen. The usual eosinophilic response may be absent in fatal helminthic infections (110, 68, 217); such an unexpected response was speculated by Opie (189) to be due to the severity of the inflammatory reaction.

Metazoan parasites which remain localized to the intestinal tract are associated with less predictable and milder degrees of eosinophilia, the eosinophilia occurring during severe infestations typically associated with periods of diarrhea and abdominal pain and probably due to significant mucosal invasion or destruction by the parasites. Thus, such eosinophilic responses may be seen during severe infestation by hookworm, strongyloides, and ascaris infestations (16). Intestinal infestations with *Enterobius vermicularis*, *Trichuris trichiura* (190), and amebiasis (124, 143) are not typically associated with eosinophilia.

Chronic infections have occasionally been reported in association with eosinophilia. Thus, Muller (181) reported that up to 10% of patients with tuberculosis had eosinophilia at some time during their disease. Similar occasional occurrence of low grade eosinophilia has been reported during intestinal tuberculosis (102), brucellosis (79), blastomycosis (202), and leprosy (202, 137). These reports have been in patients with disease characterized by multiple periods of apparent remission of the disease activity, and it has been during these periods of remission that the eosinophilia has been detected. Such instances might suggest that the eosinophilia could be a manifestation of acquired hypersensitivity, either to the pathogen itself as in the eosinophilic pneumonia of aspergillus (150) or to the drugs being administered.

Acute bacterial and viral infections are characteristically accompanied by an eosinopenic rather than an eosinophilic response, as will be discussed later. However, the development of a hypersensitivity or allergic process during the acute bacterial infection may be associated with eosinophilia with beginning resolution of the acute infection. Thus, scarlet fever (220, 90) is

associated with a mild eosinopenia during the early phase of the illness; with the appearance of the typical rash on the 4th to 5th day it may be accompanied by eosinophilia, occurring most commonly in patients with the mildest symptoms, the slightest rash, and minimal fever. Severe acute rheumatic fever is usually accompanied by eosinopenia, but when mild or accompanied by chorea or erythema multiforme eosinophilia may occur (34, 248).

Neoplastic diseases. A mild eosinophilia occurs in 5 to 10% of patients with bronchogenic carcinoma (70, 107) and is occasionally seen in other solid tumors, especially when metastatic to serosal surfaces or to bone or in tumors demonstrating central tissue necrosis (120). A mild eosinophilia is observed in about 20% of patients with Hodgkin's disease (276) and an eosinophilia as high as 90% has been reported (222, 161). Eosinophilia may accompany chronic myelocytic leukemia (276, 101, 250). The entity of "eosinophilic leukemia" will be considered with the hypereosinophilic syndromes. Eosinophilia rarely accompanies histiocytosis (eosinophilic granuloma, Hand-Schuller-Christian disease and Litterer-Siwe disease) but has been reported when there was cutaneous involvement (186, 148).

Connective tissue diseases. Eosinophilia occurs in approximately 18% of patients with periarteritis (38, 179, 275) and is especially prominent in those patients with periarteritis with pulmonary infiltrates and asthmatic symptoms (see below). It also occurs as an occasional accompaniment of severe rheumatoid arthritis (197). Recently, Shulman has described a new syndrome of diffuse fasciitis with eosinophilia (226, 205). This illness clinically resembles scleroderma or dermatomyositis and is characterized by diffuse myalgias with swelling and tenderness of the muscles of the extremities, followed by progressive stiffness with observation of firm skin tightly bound to underlying structures and development of flexion contractures of elbows and knees. The face and digits were spared and Raynaud's phenomenon was absent. Eosinophilia of 9 to 37%, elevated ESR, and hypergammaglobulinemia were present. Biopsies demonstrated absence of abnormalities of the skin or muscle, but a remarkable thickening of the deep fascia with collagenous hypertrophy and infiltration with plasma cells and lymphocytes. The etiology remains unknown, but the patients apparently have a favorable response to therapy with steroids. Because of this therapeutic response, the value of distinction of this syndrome from that of scleroderma or dermatomyositis is obvious.

The hypereosinophilic syndrome. This term refers to a group of patients who demonstrate (1) a persistent eosinophilia of 1,500 eosinophils/mm^3 for longer than 6 months or death before 6 months, associated with signs and symptoms of hypereosinophilic disease, (2) presumptive signs and symptoms of organ involvement including hepatosplenomegaly, organic heart murmur, congestive heart failure, diffuse or focal nervous system abnormalities, pulmonary fibrosis, fever, weight loss, and anemia, and (3) a lack of evidence for parasitic, allergic, or other known causes of eosinophilia (54). This group includes those previously referred to as having eosinophilic leukemia, disseminated eosinophilic collagen vascular disease, Loeffler's fibroplastic endocarditis with eosinophilia, etc. As suggested by Hardy and Anderson (104), these patients probably present a spectrum with Loeffler's disease and "eosinophilic leukemia" representing the two extremes (*Fig. 3*). The former represents a group of patients with eosinophilia with transient, migratory pulmonary infiltrates, relatively mild symptoms mainly of fever and nonproductive cough, and a self-limited course. The more severe end of the spectrum has been

FIGURE 3

Spectrum of the Hypereosinophilic Syndromes

Current terminology		Löffler's disease; pulmonary infiltration with eosinophilia syndrome	Löffler's endocarditis parietalis fibroplastica	Eosinophilic leukemia; disseminated eosinophilic collagen disease
Extent of involvement		Eosinophilia with pulmonary involvement	Eosinophilia with cardiopulmonary involvement	Eosinophilia with generalized involvement
Symptoms	Frequent	Asymptomatic; malaise; fever; cough	Malaise; fever; cough; dyspnea; weight loss	Malaise; fever; sweats; cough; dyspnea; chest pain; weight loss
	Occasional	Dyspnea	Pruritus	Pruritus
Signs	Frequent	None; transitory rales; sinus tachycardia	Sinus tachycardia; arrhythmias; cardiomegaly; murmurs; rales; edema	Sinus tachycardia; arrhythmias; cardiomegaly; murmurs; rales; edema; hepatosplenomegaly
	Occasional		Hepatosplenomegaly	Lymphadenopathy
Laboratory	Hemogram	Mild leukocytosis and eosinophilia	Mild to moderate leukocytosis and eosinophilia	Moderate to marked leukocytosis and eosinophilia; progressive anemia
	Marrow	Data scant (eosinophilic hyperplasia reported)	Data scant (eosinophilic hyperplasia when reported)	Marked granulocytic hyperplasia with eosinophilia
	Chest X ray	Transient infiltrates	Cardiomegaly; pulmonary infiltrates	Cardiomegaly; pulmonary infiltrates; pleural effusion
	Electrocardiogram		Usually abnormal but nonspecific	Usually abnormal but nonspecific (arrhythmias, ST-T changes)
Pathology	Lungs	Eosinophilic bronchitis and bronchopneumonia; granulomas; arteritis	Passive congestion; fibrosis; eosinophils	Passive congestion; granulomatous vasculitis; infiltrates of eosinophils
	Heart	Normal	Hypertrophy; mural thrombi; subendocardial fibrosis	Hypertrophy; mural thrombi focal necrosis; fibrosis; infiltrates of eosinophils
	Liver and spleen	Normal	Occasionally enlarged with eosinophilic infiltrates	Hepatosplenomegaly with infiltrates of mature eosinophils
Course		Self-limited	Generally progressive	Generally progressive
Prognosis		Recovery	Often fatal	Generally fatal

--From Hardy and Anderson, 1968 (Ref. 104)

reviewed recently by Chusid and his colleagues (54). Such patients present most frequently with weight loss, maculopapular rashes, changing mental status, hepatosplenomegaly, and signs of cardiac as well as pulmonary involvement. Although the 14 patients in the series by Chusid et al. demonstrated a remarkably benign course, the prognosis of the other 57 patients which they were able to cull from the literature had an average survival of only 9 months. Factors associated with a grave prognosis appear to be the appearance of circulating myeloblasts (all such patients died within 7 months) or a total white count of greater than 100,000/mm^3 (only 25% survived 9 months). Among their patients, Chusid and coworkers also noted that monitoring of leukemic markers (serum B_{12}, folate, leucocyte alkaline phosphatase, basophilia, and chromosomal analysis) did seem to have some predictive value, in that all of their more severely affected patients appeared to have positive findings in at least half of these leukemic criteria measured. Unlike other leukemic diseases, these patients do not die of bleeding or infection. Rather, the cause of death is most often related to the cardiac involvement, which is observed in over 95% of patients at autopsy. The most frequent cardiac manifestations included thrombi closely adherent to the endocardium, frequently fibrotic; valvular damage, usually of the mitral valve; myocardial fibrosis; myocardial necrosis with coronary

vascular thrombi; and diffuse eosinophilic infiltration of the myocardium itself. As noted by Chusid and collaborators, the mechanism of cardiac injury in this disease is unknown; however, similar cardiac lesions have been reported in eosinophilic leukemoid responses secondary to drug reactions (77) and parasitic disease (245), suggesting that the persistence of very large numbers of circulating eosinophils may be responsible.

Skin diseases. Eosinophilia may be associated with skin diseases of almost any etiology, especially pemphigus, dermatitis herpetiformis, eczema, exfoliative dermatitis, and psoriasis. As suggested by Litt (156), the frequency with which eosinophilia is seen in such disorders and the apparent lack of relationship to underlying pathophysiology of the skin lesion itself suggest that the eosinophilia may represent a part of the host response to the antigenic load appearing through the breach in the normal epidermal barrier.

Conditions with predominantly pulmonary symptoms or signs. The clinical presentation of a patient with predominantly pulmonary symptoms or the observation of pulmonary infiltrates with an associated eosinophilia may be due to many of the etiologies cited above, including allergic states, especially asthma, helminthic infections, pulmonary neoplasms, and rarely vasculitides. Conditions presenting as pulmonary infiltrates associated with eosinophilia are sufficiently distinctive and frequent to warrant further description. Since 1932 (67), such patients have usually been divided into five clinical syndromes:

(1) *Loeffler's syndrome*: Minimal to absent respiratory symptoms and fever; wandering transient pulmonary infiltrates; spontaneous recovery within one month.

(2) *Prolonged pulmonary eosinophilia*: Significant symptomatology including high fever, sweats, malaise, productive cough, chest pain; prolonged course.

(3) *Pulmonary eosinophilia with asthma*: As #2, but with superimposition of episodic bronchial obstruction.

(4) *Tropical eosinophilia*: Severe spasmodic bronchitis progressing to persistent dyspnea; malaise, weight loss, low grade fever; eosinophilia over 2,000/mm^3; positive filarial complement fixation test; good clinical response to diethylcarbamazine (74).

(5) *Periarteritis nodosa*

The current awareness that one etiologic agent may produce any of several of the syndromes depending upon host reaction and, conversely, that each syndrome is produced by multiple etiologies limits the usefulness of the clinical classification. Although Liebow and Carrington (150) considered the classification futile and suggested the term "pulmonary eosinophilia" to include all of the entities of this type, the clinical classification does provide some guidance to the approach to the individual patient.

The presentation of Loeffler's syndrome is most frequently the manifestation of an allergic response to one of a long series of drugs or chemicals, including such as penicillin, para-amino salicylic acid, acetylsalicylic acid,

nitrofurantoin, sulfonamides, chlorpropamide, and nickel carbonyl (150). Loeffler's syndrome may be the presenting manifestation of a number of invasive helminthic infections including visceral larval migrans (*Toxocara canis, Toxocara cati), Ascaris lumbricoides,* and *Strongyloides stercoralis*. It is interesting that similar pulmonary infiltrates appear to be a distant manifestation of cutaneous infection by the dog hookworm *Ancylostoma braziliense* (cutaneous larval migrans, "creeping eruption") (278). In many instances, Loeffler's syndrome will resolve prior to ascertainment of a specific etiology.

A more prolonged and severe syndrome can also be produced by drug allergies such as that to nitrofurantoin (246) and by parasitic diseases such as strongyloidiasis and filariasis (150), and has been reported during the course of tuberculosis (181) and brucellosis (79), although an unknown proportion of these may have been due to drug hypersensitivity. Many patients with prolonged pulmonary eosinophilia will have no demonstrable etiology. In addition to prolonged symptoms, such patients with "chronic eosinophilic pneumonia" developed parenchymal damage leading to restrictive lung disease (52). The radiographic picture was usually that of a migratory infiltrate; however, in some patients infiltrates appeared stable and cleared during treatment only to recur subsequently in the same region. The infiltrates were characteristically adjacent to the pleura with a clear lung field centrally, a picture which was well described as "a photographic negative of pulmonary edema" (52). Histologically, the lesions are characterized by filling of alveoli with eosinophils and large mononuclear cells and interstitial infiltrations of eosinophils, lymphocytes, and plasma cells, with occasional observation of "eosinophilic abscesses", with necrotic centers surrounded by a granulomatous capsule. They occasionally show bronchiolitis obliterans and even granulomatous reactions. Minimal microangiitis was occasionally seen but it was usually not of a necrotizing type (128).

Probably the most frequent cause of pulmonary eosinophilia with asthma is that of allergic bronchopulmonary aspergillosis (128). These patients are usually chronic asthmatics with recurrent episodes of fever, productive cough, often with blood streaked sputum, influenza like symptoms occasionally with chest pain, pulmonary infiltrates, peripheral blood eosinophilia, and small sputum plugs containing *Aspergillus fumigatus*. Radiographic findings are usually those of scattered nodular or patchy opacities. Characteristic parallel line or ring shadows, attributed to bronchial wall edema, bronchiectasis, or bronchial dilation, may be so large as to suggest cavitation. A special type of bronchiectasis characterized by dilatation of bronchi proximally with tapering distally to a normal caliber may be observed. The patients may also present with the picture of recurrent pneumonitis or atelectasis. These patients demonstrate a marked immunological reactivity to the antigens of aspergillus. Skin tests demonstrate a strong "dual" response characterized by an immediate wheal-and-flare (type I) reaction, followed in 5 to 6 hours by an arthus (type III) reaction, and concomitantly have precipitating antibodies to aspergillus in the serum. Such immunological findings are not unique to this patient population (they may occur in 33 to 90% of patients with aspergillomas). Corticosteroids have been reported to both ameliorate symptoms and hasten resolution of the infiltrates. A related syndrome may be that produced following obstruction of proximal bronchi by large plugs of inspissated mucus and exudate (128). Clinically, the great majority of such patients have chronic bronchitis or asthma with superimposed cough, fever, chest pain, hemoptysis, and upper respiratory infection, with a history of expectoration of

sputum plugs in 44%. Peripheral blood eosinophilia is frequently present but attempts to demonstrate a uniform allergen such as that of aspergillus have been inconclusive. Radiologically, the mucoid plugs may produce a sharply circumscribed round or Y-shaped density, usually in the upper lobes and frequently indistinguishable from a neoplasm. Apparently, most consider this syndrome to develop from allergic bronchitis with hypersecretion of viscid mucus (128), although other factors including excessive dehydration of secretions, excessive resorption of water by bronchial mucosa, and increased DNA content of mucus may contribute to its development. The distinction of this as a separate syndrome is valid in that the treatment involves the use of mucolytic agents such as acetyl cysteine, and corticosteroids are only rarely of benefit.

Bronchocentric granulomatosis may also be associated with asthma and eosinophilia and is characterized by granulomatous replacement of bronchial mucous membrane with adjacent pronounced eosinophilic reaction and chondritis and with exclusion of other causes of granulomatous bronchocentric lesions such as tuberculosis, invasive fungal infections, or severe rheumatoid arthritis (128). Clinically, those patients with eosinophilia within this syndrome were found to be asthmatics with an average age of 22 years with symptoms similar to those of allergic bronchopulmonary aspergillosis, although apparently less severe. Again, the radiologic observation of nodular lesions, frequently unilateral and usually in the upper lobes, or of signs of obstruction including atelectasis or consolidation, was frequent. The granulomatous inflammation contained large quantities of eosinophils, mononuclear cells and epitheloid cells with occasional foreign body giant cells. The lesions occasionally resembled Wegener's granulomatosis; the latter disorder, however, is angiocentric and is not characteristically associated with eosinophilia. Since some of the fungi that have been identified in tissue sections morphologically resemble mucor or candida and serum precipitins to *Candida albicans* were observed in one case, bronchocentric granulomatosis may represent a hypersensitivity response to fungi other than aspergillus in some asthmatics (128).

The other conditions associated with pulmonary symptoms and eosinophilia need be mentioned only briefly. Tropical eosinophilia, as defined above, is of unknown etiology. However, epidemiologic and pathologic data, the nearly uniform observation of a positive filarial complement fixation test, and the response to the antifilarial agent diethylcarbamazine strongly suggest a filarial etiology (74). With therapy, there is a disappearance of symptoms within two weeks and a fall in eosinophil count within one month. Nevertheless, it is interesting that classical filarial infection involves microfilaremia without involvement of the lung, whereas the picture of tropical eosinophilia does not involve microfilaremia. It may be that the host response in some way has localized the filariae to the lung, destroyed them in that site, but left the host with the localized chronic granulomatous reaction. Such a response is observed experimentally following the injection of trichinella larvae into rats or mice (41). Polyarteritis nodosa or other vasculitides such as those secondary to hypersensitivity response to drugs may occasionally present with pulmonary infiltrates, usually with associated asthmatic symptoms (275). Also, as mentioned above, patients with the hypereosinophilic syndrome may develop pulmonary abnormalities in about 40%, although it is uncertain what proportion of these are actually due to primary eosinophilic infiltration of the lung and what proportion are secondary to the more frequent cardiac abnormalities in this syndrome.

Conditions with predominantly gastrointestinal symptoms and signs. Early in the century it was noted that normal local intestinal eosinophil accumulation occurs following first exposure to meat in human infants (33) and that ingestion of meat is followed by increased numbers of eosinophils in the thoracic duct, whreas no increase occurs following ingestion of pure amino acids (211). Further local eosinophilic infiltration of the gut is common in inflammatory lesions of diverse etiology, including such as peptic ulcer, carcinoma, or after irradiation (238). Clinical eosinophilia may accompany a variety of gastrointestinal diseases including large infestations by essentially any metazoan parasite, regional enteritis (138), ulcerative colitis (very mild eosinophilia observed) (122), carcinoma (138), or intestinal involvement by a systemic process such as periarteritis (138) or by the hypereosinophilic syndrome (54). "Eosinophilic gastroenteritis" refers to a nodular eosinophilic infiltration of the stomach or small bowel of unknown etiology (138). The infiltrate may involve any or all layers of the gut. Although it may be prominent near vessels, neither necrotizing vasculitis nor true granuloma formation is characteristic. Symptoms depend upon the site of involvement: with predominantly mucosal disease, the patient may present with severe iron deficiency, enteric protein loss, or malabsorption. Muscle layer disease leads to marked thickening and rigidity of the gut with obstructive symptoms with radiologic features of pyloric narrowing in the stomach or features simulating regional enteritis in the small bowel. Predominantly serosal disease presents most typically as eosinophilic ascites. Although the etiology is unknown, an allergic cause is the favored hypothesis. Approximately half the patients have markedly positive personal or family histories for allergic diseases including hay fever, asthma, and urticaria. Often, specific foodstuffs have been incriminated as producing recurrent symptoms. Studies examining the effects of instillation of such a test allergen have demonstrated accentuated mucosal eosinophilia, gastric retention with hypomotility of both stomach and small intestine, coarsening of mucosal folds of the small bowel, and segmentation accompanied by the symptoms of nausea, vomiting, and abdominal pain (138). The disease appears to be a chronic relapsing process with exacerbations which may occur after asymptomatic periods of years. The response to corticosteroid therapy is generally excellent, although apparently some patients may require continued low level steroid therapy for prolonged periods.

Miscellaneous conditions associated with eosinophilia. Addison's disease is characteristically associated with a persistent mild eosinophilia. Sarcoidosis may rarely be associated with eosinophilia and massive eosinophilic pleural effusion has been reported (35). An eosinophilia accompanying pernicious anemia has usually been assumed to imply allergy to the crude liver extracts employed in the early therapy; however, an occasional eosinophilia was noted prior to the use of liver therapy (146). Following splenectomy, approximately one half of patients will develop a mild but persistent eosinophilia which may last for months (18, 17). An eosinophilia up to 23% may be seen following radiation therapy (180). Eosinophilia has been reported as an accompaniment of graft rejection (207), following peritoneal dialysis (144), and with congenital neutropenia (94). Mild persistent eosinophilia may occur as an autosomal dominant trait (184).

MECHANISMS OF EOSINOPHILIA

Associations with immunological events

Clinical eosinophilia most frequently occurs in the setting of concomitant pathophysiological stimuli of multiple immunologic and inflammatory mechanisms. Recent research has attempted to discern those aspects of these events which might have a direct relevance to the stimulus to eosinophilia. For convenience, studies of immunologic mechanisms and those of associations with specific forms of inflammation will be discussed separately. The considerations of eosinophilia as a manifestation of an immunological event have concentrated their attentions on several possibilities: (1) associations with specific immunoglobulin classes, (2) possible involvement of the eosinophil in antigen processing, (3) associations with immune complexes, and (4) the study of eosinophilia as part of a lymphocyte mediated immune response.

Associations with specific immunoglobulin classes. Eosinophilia is frequently associated with clinical conditions involving allergy of the reaginic type. Development of eosinophilia following antigenic exposure (e.g., penicillin allergy) has been correlated with skin sensitizing antibodies in man (281). Invasive parasitic infections such as trichinosis with their characteristic eosinophilia are associated with elevation of skin sensitizing antibodies (208, 260). Such observations have raised the possibility that eosinophil responses are mediated by the homocytotropic antibody. However, such associations do not establish a cause and effect relation. The studies of Walls 260), in which *Trichinella spiralis* was administered in varying form from whole larvae through to soluble antigen, were able to demonstrate discordance of the eosinophilic response and the development of skin sensitizing antibody. When animals were given intradermal soluble larval antigen, they developed skin sensitizing antibodies and anaphylactic responses on later intravenous injection of antigen without development of eosinophilia in either instance. However, there has not been any demonstration of development of eosinophilia in the absence of stimulation of tissue sensitizing antibody production in this model. As demonstrated by passive cutaneous anaphylaxis, reaginic antibodies could be detected in only 18% of rats with eosinophilia during the pulmonary granulomatous response to human gamma globulin-coated latex beads; also, there was no correlation between the height of eosinophilia and the magnitude of the reaginic response (218). Although there is an association between eosinophilia and the type of immune reaction which results in production of tissue sensitizing antibody, eosinophils probably do not have receptors for IgE or IgG (119), and there is no evidence of interaction of the cells with the antibody itself. The observations regarding the secretion of eosinophil chemotactic factor of anaphylaxis from basophils or mast cells previously sensitized with IgE provide a possible explanation for the local eosinophil accumulation at sites of IgE mediated processes; however, this in itself is not adequate to provide an explanation for a stimulus to eosinophil production and the development of systemic eosinophilia.

There is no correlation between the development of eosinophilia and the stimulation of other immunoglobulin classes (IgG, IgM or IgA) and passive transfer of large quantities of serum from eosinophilic animals does not result in a stimulus to eosinophil production.

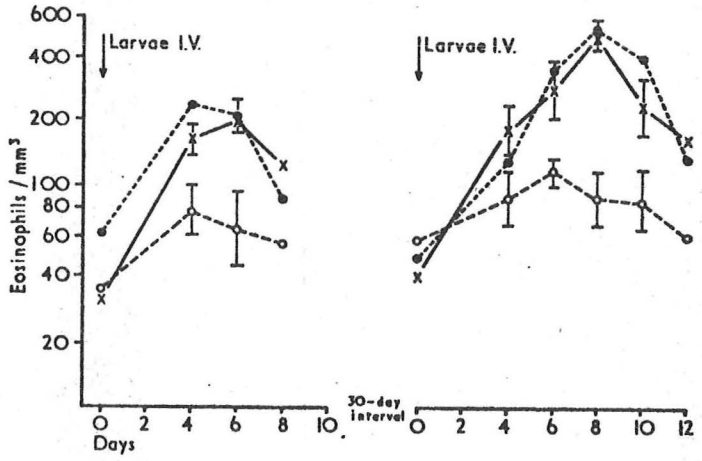
Possible involvement in antigen processing. Speirs (231) suggested the possibility that eosinophils obtain antigen from macrophages at the site of initial reaction and carry it to the site of antibody production where they are engulfed by other macrophages which are in turn somehow associated with antibody production. Eosinophils may take up antigen (203), but the amount is very small and Litt (154) did not observe one eosinophil phagocytosed by a macrophage after examination of over 15,000 lymph nodes following antigenic stimulation. Involvement of the eosinophil in antigen processing remains unproven.

Associations with immune complexes. Litt (155) and Burnet (48) viewed the eosinophil as a scavenger which disposes of antigen-antibody complexes and the by-products of their interaction. Eosinophils are attracted to and do ingest antigen-antibody complexes, as discussed previously, and Litt (154) contends that their arrest in lymph nodes during the site of antigen injection correlated with their uptake of such complexes. However, the injection of preformed complexes produces little local eosinophil accumulation unless homocytotrophic antibody is used and then the reaction is less intense than if the antibody is injected locally followed by systemic antigen, suggesting that the response is to the reaction of antigen and antibody in the tissue rather than the complex *per se* (129, 192-194). These findings apply to neutrophils as well as to eosinophils; moreover, vasculitis induced by immune complex deposition is characterized by neutrophil accumulation. Only late in the arthus reaction do eosinophils appear. Finally, accumulation of eosinophils within the lymph node may be due to a different mechanism than that observed in the tissues; thus, the local accumulation following the reaction to large polysaccharide aggregates is not blocked by immunosuppressives or x-ray (59), whereas the lymph node accumulation is blocked by antilymphocyte serum (192). It would appear that the response is more closely associated with reactions in the tissues than to the antigens, antibodies, or antigen-antibody complexes themselves.

Eosinophilia as part of a lymphocyte mediated immune response. The preceding studies have concerned local tissue and transient blood elevations of eosinophils. From the studies of eosinophil kinetics, it is apparent that these immediate events cannot represent changes in eosinophil production. However, clinical eosinophilia involves a relatively prolonged, although fluctuating, elevation of blood eosinophil levels with accelerated eosinophil production. This chronic undulating eosinophilia was first described in trichinosis by Brown in 1897 (44). Trichinosis has also proven a valuable stimulant of eosinophilia in the laboratory by oral or intravenous inoculation of the trichinella larvae in previously pathogen-free rats and mice. Following intravenous injection of muscle stage trichinella larvae, the larvae lodge in the lungs and produce a granulomatous response (40). This is associated with a delay of one to two days, followed by a burst of marrow eosinophil proliferation (240) with the resultant blood eosinophilia rising to a peak after 6 to 7 days, after which a rapid decline reflected the sharp cessation of marrow production. Following a two-week delay, a second challenge produces an augmented eosinophil response reminiscent of a secondary antibody response (27). Early studies using this model demonstrated that the eosinophilia did not correlate with the production of hemagglutinating antibody, nor could the eosinophilia be transferred with large amounts of serum (27). Attention was then directed to the lymphocyte-mediated immunological response. A series of experiments was conducted to observe the effect of suppression of known lymphocyte functions on normal eosinophil responses to larvae. Neonatal thymectomy produced a significant suppression of the eosinophilia resulting from later

inoculation with trichinosis (26). Similar suppression was observed in rats treated with antilymphocyte serum at the time of parenteral injection of larvae. Further experiments used immunosuppressive drugs with a known time-dependent action on lymphocyte functions (39). Single dose administration of such drugs to rats given intravenous larvae was found to produce a similar time-dependent suppression of the expected eosinophilia. For example, endotoxin produced suppression when given 6 hours before larvae but was without effect if given 24 hours afterward. Conversely, methotrexate produced suppression if given after 24 hours but not if given 6 hours before larvae. These observations are in accord with known effects of these agents on lymphocyte responses. If rats were lethally irradiated and then reconstituted with either thoracic duct lymphocytes or bone marrow cells or both, it was found that only the recipients of both thoracic duct cells and bone marrow cells provided a normal eosinophil response (26). In a further experiment mice were selectively depleted of thymus processed lymphocytes by lethal irradiation of thymectomized mice followed by bone marrow replacement. As a control, similar mice were reconstituted with a graft of a neonatal thymus. The following figure shows the responses of these animals to intravenous larvae (*Fig. 4*) (262). The normal and reconstituted mice produced a typical eosinophilia with enhanced response on second challenge. The T lymphocyte depleted mice did not produce an eosinophilia on either occasion.

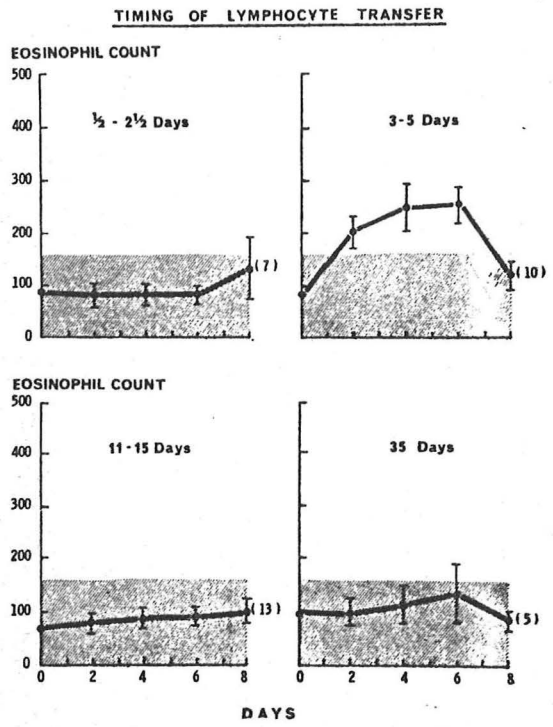
FIGURE 4



—Peripheral blood eosinophil responses (±1 standard error of the mean) to first and second intravenous injections of *T. spiralis* larvae in normal (●....●), deprived (o - - - - o), and reconstituted (x——x) mice (see text).

--From Walls, et al., 1971 (Ref. 262)

FIGURE 5



The eosinophil response to "sensitized" thoracic duct lymphocytes obtained from donors at various intervals following larval inoculation by the gastrointestinal route. Only 3–5-day collections were capable of transferring the response.

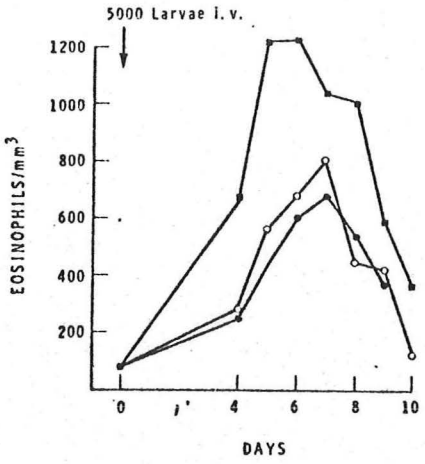
--From Basten, et al., 1970 (Ref. 27)

These experiments dealt with the suppression of the eosinophil response to larvae by various methods known to suppress the thymus processed lymphocyte population. The active transfer of the eosinophil proliferative response was also examined. Lymphocytes were collected from the thoracic duct of rats which had been given oral infestation of trichinella larvae; the lymphocytes were then injected intravenously into normal rats and eosinophil counts followed. Those thoracic duct lymphocytes obtained 3 to 5 days after larval infestation were found capable of causing an eosinophilia on transfer to normal recipients (*Fig. 5*) (27). Only live lymphocytes were able to produce this response on passive transfer. Furthermore, if the lymphocytes were enclosed in a Millipore diffusion chamber, the eosinophil response occurred as previously. These observations suggest that the thoracic duct lymphocytes produce a soluble product capable of eliciting the stimulus to eosinophilia.

The final aspect of the immunological nature of the phenomenon examined was that of antigenic specificity. The observation of an increased eosinophil response on second challenge has been mentioned. Intravenous injection of Sephadex beads produces a similar pulmonary granulomatous reaction in rats with an associated eosinophilia of a magnitude and course similar to that caused by parenteral larvae and yet caused by an unrelated antigen (264). This provided

the opportunity to test whether the enhanced secondary response would be specific for the antigen producing the initial reaction or whether the eosinophil response might be a nonspecific expression of a form of "activation" similar to that seen after macrophage stimulation. Rats were first given intravenous larvae. After a four-week delay, they were rechallenged with either another injection of larvae or an injection of a comparable dose of Sephadex beads. The second larval injection produced the expected augmented response; the injection of Sephadex after "priming" with larvae showed no increase over the first response (*Fig. 6*) (261). This suggested that the augmented eosinophilia occurring on second exposure to a stimulus is antigen specific.

FIGURE 6

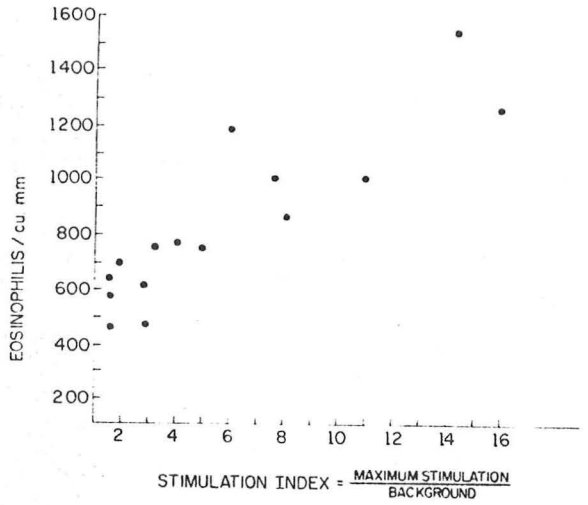


Peripheral blood eosinophils following intravenous injection of 5000 *Trichinella* larvae in unsensitized Wistar rats (●—●) and in those previously injected with *Trichinella* larvae (■—■) or with Sephadex (○—○).

--From Walls, et al., 1974 (Ref. 261)

Schriber and Zucker-Franklin have recently employed a similar model of experimental eosinophilia by intravenous injection of latex beads coated with human gamma globulin in rats (218). A pulmonary granulomatous reaction and eosinophilia occurs which is very like that seen after intravenous larvae. They observed that the height of eosinophilia correlated with a lymphocyte blast response to the specific antigen (HGG) *in vitro*, a response believed to be T lymphocyte mediated (*Fig. 7*).

FIGURE 7



Stimulation index of peripheral blood lymphocytes obtained 7 days post second injection of HGG-coated latex particles compared to the peak blood eosinophilia 5 days post second injection. Each dot represents 1 animal R+ .78.

--From Schriber and Zucker-Franklin, 1975 (Ref. 218)

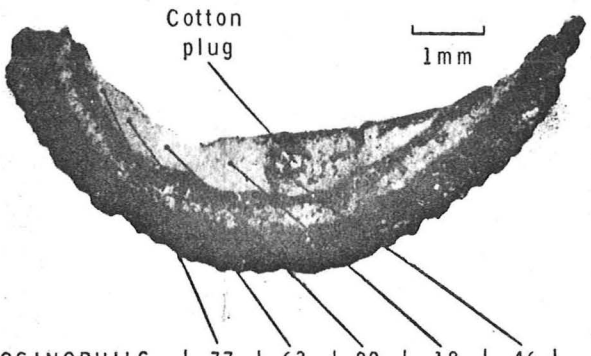
These series of experiments support the concept that eosinophilia of trichinosis is a form of immunological response. There is a latent period followed by a burst of proliferation. It is suppressed by techniques known to suppress lymphocyte responses, in particular those of the thymus processed lymphocyte population. The eosinophilia may be produced by transfer of live stimulated lymphocytes; it is not produced by transfer of serum. There is an apparent cooperation between thoracic duct lymphocytes and bone marrow cells. A second challenge produces an augmented response, and this response shows antigenic specificity.

Associations with the inflammatory response

Acute inflammation. During the initial phase of acute inflammation, eosinophils enter the region along with neutrophils. This has usually been considered a nonspecific manifestation of eosinophil response to neutrophil chemotactic agents. Yet the distribution of eosinophils at the inflammatory site is distinctive (*Fig. 8*). The neutrophils mass in greatest concentration at the inflammatory center. Here eosinophils are found in a ratio to neutrophils equal to that occurring in the bloodstream. Yet the greatest concentration of eosinophils occurs at the periphery of the inflammatory process (95, 244, 24). With persistence of the stimulus for acute inflammation, eosinophils become lsss numerous (and there is a concomitant suppression of marrow eosinopoiesis). However, as the stimulus subsides and healing of the lesion begins, the eosinophils reappear in increasing numbers (242, 220, 37, 163). This sequence is not dependent upon the type of inflammatory stimulus but occurs,

for example, in the response to myocardial infarction (163) or chemical irritants (244) as well as bacterial or viral infections (24).

FIGURE 8



EOSINOPHILS	77	63	20	18	46
NEUTROPHILS	11	10	47	132	288
% Eos	88	86	30	12	14

Distribution of eosinophils and neutrophils near an abscess of 7 h duration. The cotton plug, impregnated with staphylococci, was inserted subcutaneously in a mouse with eosinophilia. Cell counts are for areas of 0.11 mm^2. Section thickness 5 μm.

--From Bass, 1975 (Ref. 24)

Type of inflammation associated with eosinophilia. The inflammatory response following intravenous injection of *Trichinella spiralis* larvae in rats (40) and mice (260) and a similar study of the inflammatory response induced by intravenous injection of human gamma globulin coated latex particles (218) have proven convenient models for study of the inflammatory response associated with eosinophilia. These pulmonary granulomas are induced in a setting uncomplicated by preceding presence of inflammatory cells or complex parenchymal structure. These studies have also been in agreement with similar studies of the intraperitoneal exudative response to antigens such as bovine serum albumin, ragweed extract, or tetanus and diphtheria toxoid (232, 235) or *Trichinella spiralis* larvae (260). In each case, the sequence is similar, although the timing varies between species, being much more rapid in the rat. The first response is an influx of neutrophils with a concomitant small number of eosinophils. This stage reaches its peak at about 6 hours in the rat and 18 to 24 hours in the mouse and then subsides. Mononuclear cells, mainly macrophages, are present at the time of the neutrophil peak and continue to increase in number. By 12 hours in the rat and 3 days in the mouse, the lesion has become predominantly composed of mononuclear cells with numerous eosinophils, some multinucleate giant cells, and relatively few neutrophils. Basophils and mast cells are absent (218). The eosinophils tend to be more numerous in the periphery of the granulomatous response (40). In 1914, Swartz (220) noted that the eosinophils tend to localize away from the larvae, near the edge of the granulomatous reaction to trichinosis in man. A similar peripheral localization has also been observed in experimental autoimmune thyroiditis in the guinea pig (60).

Importance of a local tissue inflammatory response in the production of eosinophilia. The preceding data suggest that eosinophilia may appear as an aspect of a lymphocyte-mediated immunological response, yet it only occurs during a very limited number of such responses. Such a variable response might be a manifestation of dependence upon either the type of antigen (either hapten or carrier) and/or upon the manner of presentation of the antigen to the host. The presentation of antigen in a manner which induces a local tissue inflammatory response appears to be an important factor in the chain of events leading to stimulation of eosinophil production (27, 263). Again, the intravenous administration of *Trichinella spiralis* larvae or larval material has proven a useful model for study of this problem. Simple homogenization of larvae reduced them to a size so that they passed through the pulmonary capillaries and hence did not produce the local granulomatous reaction which follows intravenous injection of whole larvae. Injection of such homogenized larvae did not produce the usual eosinophilic response, although it resulted in an increased production of hemagglutinating antibodies. In further studies, a soluble larval extract ("larval antigen") did not produce an eosinophilia on first or second intravenous challenge, whereas the same material injected in Freund's adjuvant into the footpad did produce the typical eosinophilic response. Interestingly, the soluble larval antigen did "prime" the animals so that an augmented eosinophil response occurred when they were later given whole larvae intravenously. Thus, it appears that the memory function of the immunological response may be primed by exposure to the antigen itself, but that the stimulation of eosinophil production is dependent on a particular type of tissue inflammatory reaction rather than merely a response to a particular type of antigen.

Eosinophils and the chemical mediators of inflammation. Since 1914 (220), it has been a recurrent hypothesis that the eosinophil is not a central character in the production of the allergic or granulomatous inflammatory response, but is involved in the handling of the resultant tissue reaction (199, 202, 254, 48). Thus, the eosinophil is viewed as a scavenger, wandering around the edge of the affected area mopping up the products and preventing excessive spread. Although an appealing theory, its supporting evidence until recently has remained meager.

In 1952, Vecauteren and Peters (257) suggested that eosinophils were able to protect against histamine. R. K. Archer and his colleagues (14), studying extracts from horse eosinophils (and one experiment using a skin window study on a human volunteer), reported evidence that protein-free eosinophil extracts were able to neutralize the vasodilatory properties of histamine. They also suggested the capability of neutralization of serotonin (12) and bradykinin (15). Confirmation of these studies of vasoactive amine neutralization have not appeared. However, recent studies have provided further evidence that the eosinophil may have a homeostatic function at the site of an allergic inflammatory response. Among the numerous enzymes packed within the eosinophil granule is a large quantity of arylsulphatase. Human eosinophil arylsulphatase has been shown capable of inactivation of the slow reacting substance of anaphylaxis (267). Furthermore, the eosinophils of a patient with an active filarial infection were found to contain elevated quantities of arylsulphatase; with therapy of the infection, the eosinophil arylsulphatase levels decreased to the normal range. Hubscher (111, 112) has demonstrated that eosinophils secrete a substance which is capable of inhibition of histamine release by basophils by increasing the intracellular levels of cyclic AMP. This "eosinophil derived

inhibitor" was found to be a mixture of acidic lipids of similar physicochemical behavior and biologic activity to prostaglandins E1 and E2. Thus, the eosinophil may well play a modulatory role in the allergic inflammatory response, both by inhibiting release of the chemical mediators of inflammation and by selective inactivation of at least one of those mediators.

EOSINOPENIA

Eosinopenia is presently a rarely recognized clinical situation, as its demonstration requires the determination of an absolute eosinophil count. Nevertheless, eosinopenia occurs in limited circumstances: either situations of acute stimulation of adrenal corticosteroid release or situations of significant acute inflammatory processes, and may therefore be a clinically useful sign.

Adrenal corticosteroid effects on eosinophil behavior. In 1937, Selye (224) described the lymphopenia and lymphoid involution accompanying the nonspecific stresses of formaldehyde injection or severe exercise and, soon thereafter, the concomitant eosinopenia and neutrophilia in similar circumstances (69). The endocrine role in these events was defined by Hills, Forsham and Finch (108), who found the characteristic lymphopenia, eosinopenia, and neutrophilia after injection of ACTH in man, and then showed that this response could not be elicited in Addison's disease. The predictable nature of the eosinopenia following adrenal stimulation permitted its use as a clinical test of adrenal function (251). Following injection of ACTH, the number of circulating eosinophils drops within 4 hours by approximately 75% of normal in humans (108), and remains depressed for 12 to 24 hours. It is doubtful that eosinophils are destroyed during the response to steroids (141, 50, 113, 100). Physiologically high levels (7×10^{-5} M of cortisol are even incapable of altering the metabolic response of eosinophils to phagocytosis (57). Rather, it appears that the initial corticosteroid effect involves a reversible sequestration of eosinophils. Thus, if eosinophils were labeled by a pulse of tritiated thymidine in rats, a single dose of hydrocortisone produced transient eosinopenia, but the eosinophils which then reappeared in the blood had the same frequency of labeling and the same rate of disappearance as those in the control animals (4). Although the site of peripheral sequestration is unknown, these studies suggest that the eosinophil population returns essentially unchanged following a brief period of steroid-induced eosinopenia. It appears that the cells that remained immediately accessible to the circulation probably had entered a "marginated pool" within the vascular compartment.

With regard to concomitant events in the bone marrow, the effects observed depend on the duration and magnitude of the adrenal stimulus. A single pulse of corticosteroid at first produces no visible marrow change at the time when the eosinopenia is marked (36) and may be followed by a transient increase in the numbers of immature marrow eosinophil forms, suggesting a brief reactive increase in eosinophil production (75). Continued steroid administration for 36 hours in rats produces an increase in marrow eosinophils with preponderance of mature forms (116). Also, studies in these animals using pulse labeling with tritiated thymidine showed that a 3-day course of cortisol causes delay in appearance of mature cells, but they are then released normally on cessation of steroids (4). These studies suggest a period of delayed release of mature eosinophils from the bone marrow. With further steroid administration, the end

result is depression of eosinophil production, as shown by reduced total marrow eosinophils (91, 168, 259) and decreased mitosis rate (76, 51).

Migration of eosinophils into tissues seems to be inhibited by adrenal steroids, as observed by histological (236) and skin window studies of hypersensitivity responses (78). Inhibition of neutrophil and macrophage egress from the vascular compartment into inflammatory sites is likewise observed during steroid treatment; these effects may therefore be due to an effect on vascular endothelium rather than the leucocytes themselves.

Finally, it should be noted that there have been instances when eosinopenia following adrenal stimulation has not occurred. These have included some patients with asthma (219), generalized eczema (100), Hodgkin's disease with leukemoid reaction (100), and the hypereosinophilic syndromes (253, 80, 84). Gross (100) postulated that these states may be characterized by an exceptionally strong stimulus for eosinophilia. The mechanism of these events is unknown. Repeated attempts at its disclosure have only resulted in excluding certain possibilities. There is no evidence of a direct effect on the eosinophil. It is reasonable to suggest that steroids have their effects through mechanisms that normally affect eosinophil production and behavior. The cessation of stimulation to eosinophil production might be explained by inhibition of lymphocyte effector mechanisms. Although thymus-derived lymphocytes are not sensitive to a lethal effect of steroids except during a brief period of activation by mitogen (55), multiple effector mechanisms of activated lymphocytes may be blocked without apparent death of the lymphocytes themselves. Thus, cytotoxicity of sensitized mouse spleen cells for homologous target cells (209), cytotoxicity of rat lymphocytes on mouse target cells (58), cytotoxicity of human sensitized lymphocytes for human fibroblasts (158), and release of lymphotoxin from human lymphocytes (274) have all been inhibited by corticosteroids *in vitro*. The depression of marrow release and resultant retention of mature eosinophils is less easily explained. It is tempting to speculate that this may be related to inhibition of release of a substance such as the lymphocyte-dependent chemotactic factor for eosinophils of Cohen and Ward (63) or the inhibition of basophil release of ECFA. The mechanism of eosinophil margination during the acute response to steroids is unknown.

Eosinophil behavior during acute infection. Acute infections are typically accompanied by a marked reduction in the number of circulating eosinophils. This characteristic eosinopenia of acute infection was first described by Zappert in 1893 (280) and by 1914 Schwartz (220) was able to cite over 100 references asserting the occurrence of eosinopenia as a regular event during the acute phase of pneumonia, staphylococcal or streptococcal suppurative disease, erysipelas, epidemic meningitis (meningococcal), typhus, measles, chickenpox, rubella, cholera, and dengue. The awareness of this response is also revealed in the following poem.

THE BATTLE OF FURUNCULUS

Staphylococcus Aureus,
    By Gram and Koch he swore
He would invade new regions
    Unconquered heretofore,
By Gram and Koch he swore it--
    To take a patient's life,
And called the Cocci, young and old,
From all his colonies of gold
    To aid him in the strife.

Loud rang the warning toxins,
    And flashed the summons forth
On the distant slopes of Agar
    And the turbid seas of Broth;
The Cocci clustered thickly
    From far-off lands and labs.
Cocci of ancient culture came,
To come by tube they thought no shame,
But others of a fiercer fame
    Drove up in acne scabs.

The septic hosts of Cocci
    Advanced in serried ranks,
They marched upon the Blood Stream,
    And camped upon its banks;
Forth flew the watchful blood-cells
    Crying in wild turmoil:
"Staphylococcus Aureus
    "Has come and raised a boil!"

Far down the purple current
    Was borne the direful shout--
The polymorphonuclears
    And lymphocytes rush out;
Shame on the Eosinophil,
    Who comes not forth to foil
The deadly Golden Coccus
    At the Battle of the Boil!

And fiercely raged the conflict,
    And thick lay strewn the dead;
The Battle of Furunculus
    Was coming to a head!
The pale and lifeless pus cells
    In scores were borne away,
But not a single Coccus
    Survived that bloody fray.

Staphylococcus Aureus
    Still wields his golden chain,
Where falling in the central slough
    His friends around lie slain;
Surrounded and outnumbered
    Still valiantly he fights--
He sees his tawny hosts grow less,
He sees the battle's hopelessness,
Yet ever through the Yellow Press
    Defies the leucocytes.

Staphylococcus Aureus
    Has fallen in the fray,
Upon a martial coverslip
    They bore his corpse away--
Lying in state in Canada
    Embalmed he long remained,
For though he dyed Gram positive
    His honour was unstained.

And still at festive seasons,
    When the blood is really stirred,
Before the full post-prandial rise
    Of white cells has occurred,
When the phagocytes sit waiting
    With platelets undersized
For the evening meal of microbes
    Which is being opsonized;

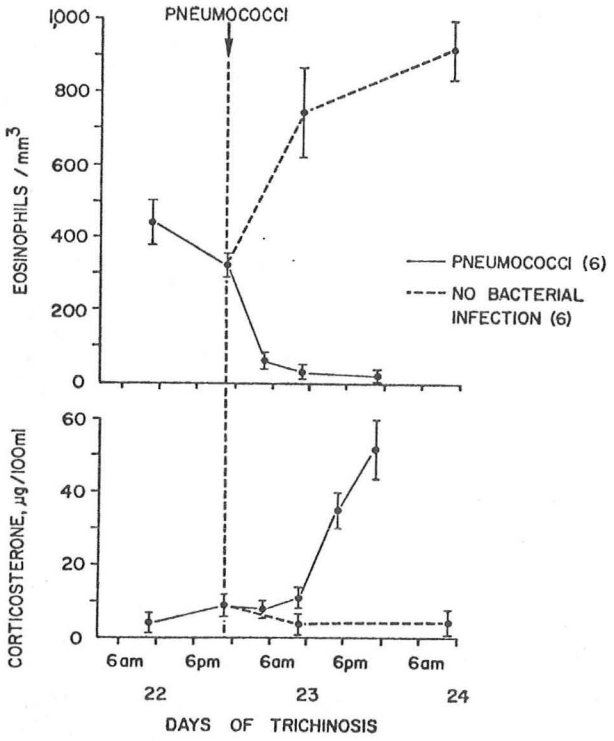
When the trembling Eosinophile
    That wrought the deed of shame,
Immune from fresh invasion
    Comes forth his share to claim,
And talks of Staphylococcus,
    And mocks his ancient fame
(For now the Yellow Peril
    Is nothing but a name);

Some old and hoary leucocyte,
    Who finds he's in the vein,
Will tell the well-known story
    Of his battles once again;
While blood cells sit in rouleaux round
    To hear the tale re-told
Of the battle of Furunculus
    In the brave days of old.

R.B.P., Oct., 1909

In 1934, Spink (237) demonstrated that infection with staphylococci, tubercle bacilli or trypanosomes could even obliterate the strong eosinophilia induced by trichinosis in guinea pigs. The eosinopenic response occurs abruptly with the onset of acute infection in eosinophilic mice with trichinosis; the superimposition of a pneumococcal infection produces a remarkable drop in eosinophil counts within six hours after inoculation of the pneumococci (*Fig. 9*).

FIGURE 9



Response to pneumococcal abscess in mice with trichinosis. Serum corticosterone and eosinophil counts after inoculation of subcutaneous air pouches with pneumococci or saline (mean±SEM).

--From Bass, 1975 (Ref. 23)

This eosinopenic response is not dependent on adrenal corticosteroid stimulation as it precedes the rise in serum glucocorticoids and occurs normally in adrenalectomized animals (23). During the initial response to acute infection, there is a remarkable influx of eosinophils into the acute inflammatory site, as discussed above, which may be sufficient to account for this initial eosinopenia. However, as the acute infection continued, there is also an apparent inhibition of eosinophil egress from the bone marrow with a build-up of mature, non-dividing eosinophils within the marrow space and later an inhibition of eosinophil production within the marrow. At least the initial eosinopenic response may be duplicated by passive transfer of a material obtained from the acute inflammatory exudate (22). Although this material has not been well characterized, preliminary experiments suggest that it may be a large glycoprotein. With cure of the acute infection, normal dynamics for eosinophilia

are restored, and eosinophil levels promptly return to normal (24). As discussed above, eosinophils reappear in the inflammatory exudate during the period of healing. This reappearance of eosinophils has been reported as occasionally progressing to a transient eosinophilia, the "reactive eosinophilia" of Staubli (242) following the natural termination of a variety of acute infections; however, these patients had been on a variety of treatment regimens and the resolution of the acute infection may merely have unmasked a hypersensitivity which had developed during the treatment or some pre-existing hypereosinophilic state. Eosinophil dynamics during the healing phase of acute inflammation have not been examined since the first part of this century. Considering the current speculations that the eosinophil functions as a homeostatic cell in the control of the inflammatory process, these "classical" observations need to be re-examined.

CONCLUSION

What generalizations may be drawn from this diversity of observations? Most of the distinctive aspects of eosinophil structure and behavior remain descriptive and the role of this enigmatic cell continues a source for speculation. The most distinctive structural qualities reside in the eosinophil granules. Although a function of arylsulphatase--the inactivation of SRS-A--has been suggested, the function of the two greatest components of the granule, peroxidase and the basic protein, are unknown. The eosinophil shares many properties with the neutrophil, including phagocytosis and even bactericidal activity, but it performs these so inefficiently that it is doubtful that they represent a central function of the eosinophil.

Many functions have been suggested for the eosinophil, including antigen processing, detoxification of immune complexes, regulation of IgE production and defense against parasitic infection. These have been discussed and the evidence for each remains inadequate. More appealing is the recurrent speculation of the past 60 years--that the eosinophil is a homeostatic cell, helping to suppress excessive stimuli to inflammation and preventing unnecessary spread of the inflammatory process. Although all aspects of such a homeostatic role require further delineation, much of what is known of eosinophil behavior is compatible with this hypothesis. The eosinophil tends to localize at the periphery of acute and chronic inflammation, where such a modulatory role would be desirable. It is suppressed with a strong stimulus to acute inflammation, but reappears as the acute stimulus subsides, the acute process regresses and healing begins. Further eosinophil stimulation occurs when the inflammatory process is magnified by hypersensitivity to a pathological state. Here, certain inhibitory functions have been suggested--the eosinophil may inhibit histamine release and it may deactivate one of the mediators of the hypersensitivity state, SRS-A. There has been little study of possible eosinophil inhibition of the other inflammatory cells; apparently it may inhibit neutrophil chemotaxis under certain circumstances. Possible effects on the lymphocyte have not been examined; in light of the close correlation of eosinophilia with lymphocyte-mediated responses, such a study is obviously needed.

Clinical eosinophilia usually suggests the presence of a combined stimulation of local inflammatory and immunological mechanisms, most often observed in a setting of persistent or repeated antigen exposure and especially when the process occurs at a skin or mucosal surface. Clinical eosinopenia suggests the

presence of significant acute stress to stimulate adrenal corticosteroid production or the presence of an acute inflammatory process as in a bacterial or viral infection. An absolute eosinophil count is required for an accurate estimate of circulating eosinophils and may provide a significant adjunct in differential diagnosis, for example in the patient with fever. Detailed observations of clinical eosinophil changes have not appeared for nearly a half-century. A renewed interest in clinical and histological studies of eosinophil behavior could suggest fundamentally new research approaches for the further clarification of the function of this elusive cell.

REFERENCES

1. Adami, J. G. 1909. An Introduction to the Study of Pathology. Macmillan & Co., London.

2. Alexander, P., Monette, F. C., LoBue, J., Gordon, A. S., and Chan, P. C. 1969. Mechanisms of leukocyte production and release. X. Eosinophil proliferation in rats of different ages. Scand. J. Haemat. 6:310.

3. Anderson, V., and Bro-Rasmussen, F. 1968. Autoradiographic studies of the kinetics of eosinophils. Ser. Haemat. 1:33.

4. Anderson, V., Bro-Rasmussen, F., and Hougaard, K. 1969. Autoradiographic studies of eosinophil kinetics: Effects of cortisol. Cell & Tissue Kinetics 2:139.

5. Archer, G. T. 1968. The function of the eosinophil. Bibl. Haemat. 29,pt 1: p. 71.

6. Archer, G. T., and Blackwood, A. 1965. Formation of Charcot-Leyden crystals in human eosinophils and study of the composition of the isolated crystals. J. Exp. Med. 122:173.

7. Archer, G. T., and Bosworth, N. 1961. Phagocytosis by eosinophils following antigen-antibody reactions *in vitro*. Aust. J. Exp. Biol. Med. Sci. 39:157.

8. Archer, G. T., and Hirsch, J. G. 1963. Isolation of granules from eosinophil leukocytes and study of their enzyme content. J. Exp. Med. 118:277.

9. Archer, G. T., and Hirsch, J. G. 1963. Motion picture studies on degranulation of horse eosinophils during phagocytosis. J. Exp. Med. 118:287.

10. Archer, G. T., and Jackas, M. 1965. Disruption of mast cells by a component of eosinophil granules. Nature (Lond.) 205:599.

11. Archer, G. T., Air, G., Jackas, M., and Morell, D. B. 1965. Studies on rat eosinophil peroxidase. Biochim. Biophys. Acta 99:96.

12. Archer, R. K. 1959. Eosinophil leukocytes and their reactions to histamine and 5 hydroxytryptamine. J. Path. Bact. 78:95.

13. Archer, R. K. 1960. Eosinophil leukocyte-attracting effect of histamine in skin. Nature (Lond.) 187:155.

14. Archer, R. K. 1968. The eosinophil leukocytes. Ser. Haemat. 1:3.

15. Archer, R. K., and Broome, J. 1963. Bradykinin and eosinophils. Nature (Lond.) 198:893.

16. Ashford, B. K., Payne, G. C., and Payne, F. K. 1933. Acute uncinariasis from massive infestation and its implications. JAMA 101:843.

17. Ask-Upmark, E. 1935. The remote effects of the removal of the normal spleen in man. Acta Soc. Med. Suecanae, Stockholm, 61:197.

18. Audibert, V., and Vallette, P. 1907. Eosinophilie après splénectomie. Compte Rend. Soc. Biol. 62:536.

19. Baehner, R. L., and Johnston, R. B., Jr. 1971. Metabolic and bactericidal activities of human eosinophils. Brit. J. Haemat. 20:277.

20. Bainton, D. F., and Farquhar, M. G. 1967. Segregation and packaging of granule enzymes in eosinophils (abstract). J. Cell. Biol. 35:6A.

21. Barnhart, M. I., and Riddle, J. M. 1965. Cellular localization of profibrinolysin (plasminogen). Blood 21:306.

22. Bass, D. A. 1973. Behavior of the eosinophil leukocyte in acute inflammation. Thesis for degree of Doctor of Philosophy, Oxford University.

23. Bass, D. A. 1975. Behavior of eosinophil leukocytes in acute inflammation. I. Lack of dependence on adrenal function. J. Clin. Invest. 55:1229.

24. Bass, D. A. 1975. Behavior of eosinophil leukocytes in acute inflammation. II. Eosinophil dynamics in acute inflammation. J. Clin. Invest. *(in press)*

25. Basten, A. 1969. The mechanism of eosinophilia in parasitic infestation. Thesis for degree of Doctor of Philosophy, Oxford University.

26. Basten, A., and Beeson, P. B. 1970. Mechanism of eosinophilia. II. Role of the lymphocyte. J. Exp. Med. 131:1288.

27. Basten, A., Boyer, M. B., and Beeson, P. B. 1970. Mechanism of eosinophilia. I. Factors affecting the eosinophil response of rats to *Trichinella spiralis*. J. Exp. Med. 113:1271.

28. Bayne-Jones, S. 1916. Pleural fluid eosinophilia. Report of a case. Bull. Johns Hopkins Hosp. 27:12.

29. Beckerdite, S., Mooney, C., Weiss, J., Franson, R., and Elsbach, P. 1974. Early and discrete changes in permeability of Escherichia coli and certain other gram-negative bacteria during killing by granulocytes. J. Exp. Med. 140:396.

30. Behrens, M., and Marti, H. R. 1962. Gewinnung der "eosinophilen Substanz" aus isolierten eosinophilen Granulozyten des pferdebluttes. Biochim. Biophys. Acta 65:551.

31. Beisel, W. R., and Rappoport, M. I. 1969. Interrelations between adrenocortical functions and infectious illness. N. Engl. J. Med. 280:541.

32. Bennett, I. L. 1951. Comparison of leukocyte changes produced by pyrogens and by anaphylaxis in guinea pigs. Proc. Soc. Exp. Biol. Med. 77:772.

33. Berger, H. C. 1916. Eosinophilia occurring in infants following the ingestion of foreign protein. Arch. Pediat. 33:742.

34. Berger, H. C. 1921. Eosinophilia occurring in chorea. Am. J. Dis. Child. 21:477.

35. Berté, S. J., and Pfutennauer, M. A. 1962. Massive pleural effusion in sarcoidosis. Am. Rev. Resp. Dis. 86:261.

36. Best, W. R., and Samter, M. 1951. Variation and error in eosinophil counts of blood and bone marrow. Blood 6:61.

37. Biggart, J. H. 1932. Some observations on the eosinophil cell. J. Path. Bact. 35:799.

38. Blackburn, C. R. 1950. Periarteritis nodosa simulating eosinophilic leukemia. Am. J. Med. Sci. 220:313.

39. Boyer, M. B., Basten, A., and Beeson, P. B. 1970. Mechanism of eosinophilia. III. Suppression of eosinophilia by agents known to modify the immune response. Blood 36:458.

40. Boyer, M. B., Spry, C.J.F., Beeson, P. B., and Sheldon, W. H. 1971. Mechanism of eosinophilia. IV. The pulmonary lesion resulting from intravenous injection of *Trichinella spiralis*. Yale J. Biol. Med. 43:351.

41. Breton-Gorius, J. 1966. Structures periodiques dans les granulations des leukocytes polynucléares du sang de l'homme. Nouv. Rev. Franc. Hemat. 6:195.

42. Bro-Rasmussen, F., Anderson, V., and Henrickson, O. 1967. The kinetics of eosinophil granulocytes in rats. Autoradiographic studies. Scand. J. Haemat. 4:81.

43. Brown, T. R. 1897. Studies in trichinosis. Johns Hopkins Med. Bull. 8:79.

44. Brown, T. R. 1898. Studies on trichinosis with special reference to the increase of the eosinophilic cells in the blood and muscle, the origin of these cells and their diagnostic importance. J. Exp. Med. 3:315.

45. Bosworth, N., and Archer, G. T. 1962. Phagocytosis-promoting substance present in eosinophils. Aust. J. Exp. Biol. Med. Sci. 40:277.

46. Buckley, R. H., Wray, B. B., and Belmaker, E. Z. 1972. Extreme hyperimmunoglobulinemia E and undue susceptibility to infection. Pediatrics 49:59.

47. Bujak, J. S., and Root, R. K. 1974. The role of peroxidase in the bactericidal activity of human blood eosinophils. Blood 43:727.

48. Burnet, F. M. 1969. Cellular Immunology. Cambridge Univ. Press, London, p. 158.

49. Caldwell, J. H., Tennenbaum, J. I., and Bronstein, H. A. 1970. Serum IgE in eosinophilic gastroenteritis. Response to challenge. N. Engl. J. Med. 292:1388.

50. Cape, R.D.T., Thomas, J. W., and Palmer, R. A. 1952. The effect of adrenal steroids on eosinophils. Canad. Med. Assn. J. 66:441.

51. Cardinelli, G., Cardinelli, G., DeCaro, B. M., Handler, A. H., and Aboul-Enein, M. 1964. Effect of high doses of cortisone on bone marrow cell proliferation of the syrian hamster. Cancer Res. 24:969.

52. Carrington, C., Addington, W., Goff, A., Madoff, I., Marks, A., Schwaber, J., and Gaensler, E. 1969. Chronic eosinophilic pneumonia. N. Engl. J. Med. 280:787.

53. Cartwright, G. E., Athens, J. W., Haab, O. P., Raab, S. O., Boggs, D. R., and Wintrobe, M. M. 1963-64. Blood granulocyte kinetics in conditions associated with granulocytosis. Ann. N. Y. Acad. Sci. 113:963.

54. Chusid, M. J., Dale, D. C., West, B. C., and Wolff, S. M. 1975. The hyper-eosinophilic syndrome: Analysis of fourteen cases with review of the literature. Medicine 54:1.

55. Claman, H. N. 1972. Corticosteroids and lymphoid cells. N. Engl. J. Med. 287:388.

56. Cline, M. J. 1972. Microbicidal activity of human eosinophils. J. Retic. Soc. 12:332.

57. Cline, M. J., Hanifen, J., and Lehrer, R. I. 1968. Phagocytosis by human eosinophils. Blood 32:922.

58. Cohen, I. R., Stavy, L., and Feldman, M. 1970. Glucocorticoids and cellular immunity *in vitro*: facilitation of the sensitization phase and inhibition of the effector phase of a lymphocyte anti-fibroblast reaction. J. Exp. Med. 132:1055.

59. Cohen, N. S., LoBue, J. L., and Gordon, A. S. 1967. Mechanisms of leukocyte production and release. VIII. Eosinophil and neutrophil kinetics in rats. Scand. J. Haemat. 4:339.

60. Cohen, S., Rose, N. R., and Brown, R. C. 1974. The appearance of eosinophils during the development of experimental autoimmune thyroiditis in the guinea pig. Clin. Immunol. Immunopathol. 2:256.

61. Cohen, S. G., and Sapp, T. M. 1963. Experimental eosinophilia. IV. Eosinotactic influences of polysaccharides. Exp. Molec. Path. 2:74.

62. Cohen, S. G., and Sapp, T. M. 1969. Phagocytosis of bacteria by eosinophils in infectious-related asthma. J. Allerg. 44:113.

63. Cohen, S., and Ward, P. A. 1971. *In vitro* and *in vivo* activity of a lymphocyte and immune-complex dependent chemotactic factor for eosinophils. J. Exp. Med. 133:133.

64. Cohn, D. A., Athanassiades, T. J., and Speirs, R. S. 1974. Inflammatory cell responses to antigen in thymus deprived mice: Reduced eosinophils and mononuclear cells. J. Retic. Soc. 15:199.

65. Colley, D. C. 1973. Eosinophils and immune mechanisms. I. Eosinophil stimulation promoter (ESP): A lymphokine induced by specific antigen or phytohemagglutinin. J. Immunol. 110:1419.

66. Cotran, R. S., and Litt, M. 1969. The entry of granule-associated peroxidase into the phagocytic vacuoles of eosinophils. J. Exp. Med. 129: 1291.

67. Crofton, J. W., Livingstone, J. L., Oswald, N. C., and Roberts, A.T.U. 1932. Pulmonary eosinophilia. Thorax 7:1.

68. Cutler. 1902. Eosinophilia in a recent case of trichinosis. Trans. Assn. Am. Phys. 17:356.

69. Dalton, A. J., and Selye, H. 1939. The blood picture during the alarm reaction. Folia Haematol. 62:397.

70. Dellon, A. L., Hume, R. B., and Chretien, P. B. 1974. Eosinophilia in bronchogenic carcinoma. N. Engl. J. Med. 291:207.

71. Discombe, G. 1946. Criteria of eosinophilia. Lancet 1:195.

72. Dixon, H.B.F., and Smithers, D. W. 1934. Epilepsy in cysticercosis (Taenia solium). Quart. J. Med. 2:603.

73. Domarus, A. 1931. Die Bedeutung der Kammerzählung der Eosinophilen für die Klinik. Deutsch. Arch. klin. Med. 171:24.

74. Donohugh, D. L. 1963. Tropical eosinophilia: An etiologic inquiry. N. Engl. J. Med. 269:1357.

75. Durgin, M. L., and Meyer, R. K. 1951. Effect of adreno-cortical extracts on bone marrow eosinophils of mice. Endocrinology 48:518.

76. Dustin, P., and deHarven, E. 1954. Le regulation hormonale de l'eosinophile sanguine et son mechanism. Rev. d'Hemat. (Brussels) 9:307.

77. Edge, J. R. 1946. Myocardial fibrosis following arsenical therapy. Lancet 2:676.

78. Eidinger, D., Wilkinson, R., and Rose, B. 1964. A study of cellular responses in immune reactions using skin window technique. I. Immediate hypersensitivity reactions. J. Allergy 35:77.

79. Elsom, K. A., and Ingelfinger, F. J. 1942. Eosinophilia and pneumonitis in chronic brucellosis: a report of two cases. Ann. Intern. Med. 16:995.

80. Engfeldt, B., and Zetterstrom, R. 1956. Disseminated eosinophilic "collagen disease". Acta Med. Scand. 153:337.

81. Enomoto, T., and Kitani, T. 1966. Electron microscopic studies on peroxidase and acid phosphatase reaction in human leukocytes. Acta Haematol. Jap. 29: 554.

82. Esselier, A. F., Jeanneret, P., Kopp, E., and Morandi, L. 1954. Evidence against destruction of eosinophils by glucocorticoids by *in vitro* experiments. Endocrinology 54:477.

83. Felarca, A. B., and Lowell, F. C. 1968. Failure to elicit histamine eosinophilotaxis in the skin of atopic man. Description of an improved technique. J. Allergy 14:82.

84. Fernex, M., and Riley, J. F. 1968. The Mast Cell System. Its Relationship to Atherosclerosis, Fibrosis and Eosinophils. S. Karger, Basel, p. 145.

85. Fiessinger, N. 1916. La defense leucocytaire dans la place de guerre. Arch. Med. Exp. d'anat. Path. 27:270.

86. Finney, D. J. 1950. *In* Biological Standardization, 2nd Ed., by Burn, J. H., Finney, D. J., and Goodwin, L. G. Oxford University Press, London, p. 72.

87. Foot, E. C. 1963. Eosinophil turnover in the rat. Nature (Lond.) 198:297.

88. Foot, E. C. 1965. Eosinophil turnover in the normal rat. Brit. J. Haemat. 11:439.

89. Ford, R. M. 1966. Transient pulmonary eosinophilia and asthma: review of 20 cases occurring in 5702 asthma sufferers. Am. Rev. Resp. Dis. 93:797.

90. Friedman, S. 1935. Eosinophilia in scarlet fever. Am. J. Dis. Child. 49:933.

91. Fruhman, G. J., and Gordon, A. S. 1955. A quantitative study of adrenal influences upon cellular elements of the bone marrow. Endocrinology 57: 711.

92. Fuerst, D. E., and Jannach, J. R. 1965. Autofluorescence of eosinophils: a bone-marrow study. Nature (Lond.) 205:1333.

93. Ghidoni, J. J., and Goldberg, A. F. 1966. Light and electron microscopic localization of acid phosphatase activity in human eosinophils. Am. J. Clin. Path. 45:402.

94. Gilman, P. A., Jackson, D. P., and Guild, H. G. 1970. Congenital agranulocytosis: Prolonged survival and terminal acute leukaemia. Blood 36:576.

95. Glaser, R. J., and Wood, W. B. 1951. Pathogenesis of streptococcal pneumonia in the rat. AMA Arch. Path. 52:244.

96. Gleich, G. J., Loegering, D. A., and Maldonado, J. E. 1973. Identification of a major basic protein in guinea pig eosinophil granules. J. Exp. Med. 137:1459.

97. Gollasch. 1889. Zur Kenntniss der asthmatischen Sputums. Ftschr. d. Medizin (Berlin) 7:361.

98. Gordon, A. S. 1955. Aspects of hormonal influences on the leukocytes. Ann. N. Y. Acad. Sci. 59:907.

99. Greenwood, B. 1968. The motility of sheep, human and pig eosinophil leukocytes *in vitro*. J. Physiol. 196:108.

100. Gross, R. 1962. The eosinophils. *In* The Physiology and Pathology of the Leukocytes. Edited by H. Braunsteiner and D. Zucker-Franklin. Grune and Stratton, New York, p. 1.

101. Gruenwald, H., Kiossoglou, K. A., Mitus, W. J., and Dameshek, W. 1965. Philadelphia chromosome in eosinophilic leukemia. Am. J. Med. 39:1003.

102. Hahn, F. 1922. Über Eosinophilie in Kindesalter. Ztschr. f. Kinderh. 34:165.

103. Hahn, F. 1967. Anaphylatoxin and anaphylaxis. Allergeology, Proc. 6th Cong. Int. Assn. Allergeology, Montreal. Excerpta Med. Int. Cong. Ser. 162:145.

104. Hardy, W. R., and Anderson, R. E. 1968. The hypereosinophilic syndromes. Ann. Intern. Med. 68:1220.

105. Harris, H. 1954. Role of chemotaxis in inflammation. Phys. Rev. 34:529.

106. Harris, P. F., Haigh, G., and Watson, B. 1961. Microradiography of cells in smears of bone marrow and lymphoid tissue. Acta Haemat. 26:154.

107. Healy, T. M. 1974. Eosinophilia in bronchogenic carcinoma (Letter). N. Engl. J. Med. 291:794.

108. Hills, A. G., Forsham, P. H., and Finch, C. A. 1948. Changes in circulating leukocytes induced by the administration of pituitary adrenocorticotrophic hormone in man. Blood 3:755.

109. Hirsch, J. G. 1965. Neutrophil and eosinophil leukocytes. *In* The Inflammatory Process. Edited by B. W. Zweifach, L. Grant, and R. T. McCluskey. Academic Press, New York, p. 245.

110. Howard, W. T. 1899. Report of a fatal case of trichinosis without eosinophilia, but with large numbers of eosinophilic cells in the muscle lesions; with remarks on the origin of the eosinophilic cells in trichinosis. Philadelphia Med. J. 4:1085.

111. Hubscher, T. 1975. Role of the eosinophil in the allergic reactions. I. EDI--An eosinophil-derived inhibitor of histamine release. J. Immunol. 114:1379.

112. Hubscher, T. 1975. Role of the eosinophil in the allergic reactions. II. Release of prostaglandins from human eosinophilic leukocytes. J. Immunol. 114:1389.

113. Hudson, B. 1954. The effects of 17-hydroxycorticosterone (compound F) on human eosinophils. Aust. J. Exp. Biol. 32:601.

114. Hudson, G. 1963. Changes in the marrow reserve of eosinophils following re-exposure to foreign protein. Brit. J. Haemat. 9:446.

115. Hudson, G. 1964. The marrow reserve of eosinophils: effect of cortical hormones on the foreign protein response. Brit. J. Haemat. 10:122.

116. Hudson, G. 1966. Eosinophil granulocyte reactions. *In* Bone Marrow Reactions. Edited by J. M. Yoffey. Edward Arnold, London, p. 86.

117. Hudson, G. 1968. Quantitative study of eosinophil granulocytes. Semin. Haemat. 5:166.

118. Ishikawa, T., Wicher, K., and Arbesman, C. E. 1974. In vitro and in vivo studies on uptake of antigen-antibody complexes by eosinophils. Int. Arch. Allergy & Appl. Immunol. 46:230.

119. Ishizaka, K., Tomioka, H., and Ishizaka, T. 1970. Mechanisms of passive sensitization. I. Presence of IgE and IgG molecules on human leukocytes. J. Immunol. 105:1459.

120. Isaacson, N. H., and Rapoport, P. 1946. Eosinophilia in malignant tumors. Ann. Int. Med. 25:893.

121. Jensen, J. 1967. Anaphylatoxin and its relation to the complement system. Science (Wash.) 155:1122.

122. Juhlin, L. 1963. Basophil and eosinophil leukocytes in various internal disorders. Acta Med. Scand. 174:249.

123. Kagan, I. L. 1960. Trichinosis: A review of biologic, serologic and immunologic aspects. J. Inf. Dis. 107:65.

124. Kampmeier, R. H., and Hineman, E. H. 1937. Amebic dysentery. J. Lab. Clin. Med. 22:985.

125. Kaplan, M. H., and Dienes, L. 1959. The cellular response in forms of delayed- and immediate-type skin reactions in the guinea pig. *In* Mechanisms of Hypersensitivity, Henry Ford Hosp. Int. Symposium. Little, Brown & Co., Boston, p. 435.

126. Kaplow, L. S. 1965. Simplified myeloperoxidase stain using benzidine dihydrochloride. Blood 26:215.

127. Katz, A. M., and Pan, C.-T. 1958. Echinococcus disease in the United States. Am. J. Med. 25:759.

128. Katzenstein, A.-L., Liebow, A. A., and Friedman, P. J. 1975. Bronchocentric granulomatosis, mucoid impaction, and hypersensitivity reactions to fungi. Am. Rev. Resp. Dis. 111:497.

129. Kay, A. B. 1970. Studies on eosinophil leukocyte migration. 1. Eosinophil and neutrophil accumulation following antigen-antibody reactions in guinea-pig skin. Clin. Exp. Immunol. 6:75.

130. Kay, A. B. 1970. Studies on eosinophil leukocyte migration. II. Factors specifically chemotactic for eosinophils and neutrophils generated from guinea-pig serum by antigen-antibody complexes. Clin. Exp. Immunol. 7:723.

131. Kay, A. B., and Austen, K. F. 1971. The IgE-mediated release of an eosinophil leukocyte chemotactic factor from human lung. J. Immunol. 107:899.

132. Kay, A. B., Stechschulte, D. J., and Austen, K. F. 1971. An eosinophil leukocyte chemotactic factor of anaphylaxis. J. Exp. Med. 133:602.

133. Kay, A. B., Shin, H. S., and Austen, K. F. 1973. Selective attraction of eosinophils and synergism between eosinophil chemotactic factor of anaphylaxis (ECF-A) and a fragment cleaved from the fifth component of complement. Immunology 24:969.

134. Kellaway, C. H., and Fairley, K. D. 1932. The clinical significance of laboratory tests in the diagnosis of hydatid disease. Med. J. Aust., p. 340.

135. Keller, H. U., and Sorkin, E. 1969. Studies on chemotaxis. XIII. Differences in chemotactic responses of neutrophil and eosinophil polymorphonuclear leukocytes. Int. Arch. Allergy 35:279.

136. Kellermeyer, R. W., and Warren, K. S. 1971. The role of chemical mediators in the inflammatory response induced by foreign bodies. Comparison with the schistosome egg granuloma. J. Exp. Med. 131:21.

137. Kiang, S., and Choa, G. H. 1949. The blood picture in leprosy. Am. J. Med. Sci. 217:269.

138. Klein, N. C., Hargrove, R. L., Sleisenger, M. H., and Jeffries, G. H. 1970. Eosinophilic gastroenteritis. Medicine 49:299.

139. Kline, P. S., Cohen, M. B., and Rudolph, J. A. 1932. Histologic changes in allergic and non-allergic wheals. J. Allergy 3:531.

140. Kostage, S. T., Rizzo, A. P., and Cohen, S. G. 1967. Experimental eosinophilia. XI. Cell response to particles of delineated size. Proc. Soc. Exp. Biol. Med. 125:413.

141. Krippaehne, M. L., and Osgood, E. E. 1955. Studies of the influence of cortisone and hydrocortisone on human leukocytes in culture and in eosinophilic leukaemia. Acta Haemat. 13:145.

142. Lachmann, P. J., Kay, A. B., and Thompson, R. A. 1970. The chemotactic activity for neutrophil and eosinophil leukocytes of the trimolecular complex of the fifth, sixth and seventh components of human complement (C567) prepared in free solution by the "reactive lysis" procedure. Immunology 19:895.

143. Lamont, N. M., and Pooler, N. R. 1958. Hepatic amoebiasis. Quart. J. Med. 27:389.

144. Lee, S., and Schoen, I. 1967. Eosinophilia of peritoneal fluid and peripheral blood associated with chronic peritoneal dialysis. Am. J. Clin. Path. 47:638.

145. Lehrer, R. I., and Cline, M. J. 1968. Absent myeloperoxidase and leukocyte candidacidal activity in a patient with systemic candidiasis. Clin. Res. 16:331.

146. Levine, S. A., and Ladd, W. S. 1921. Pernicious anemia: Clinical study of one hundred and fifth consecutive cases with special reference to gastric anacidity. Bull. Johns Hopkins Hosp. 32:254.

147. Leyden, E. 1872. Zur Kenntis des Bronchial-Asthma. Virchow's Arch. Path. Anat. 54:324.

148. Liao, K. T., Rosai, J., and Dameshek, K. 1972. Malignant histiocytosis with cutaneous involvement and eosinophilia. Am. J. Clin. Path. 57:438.

149. Lichtenstein, L. M., Gewurz, H., Adkinson, N. F., Jr., Shin, H. S., and Mergenhagen, S. E. 1969. Interactions of the complement system with endotoxic polysaccharide. The generation of an anaphylatoxin. Immunology 16:327.

150. Liebow, A. A., and Carrington, C. B. 1969. The eosinophilic pneumonias. Medicine 48:251.

151. Litt, M. 1960. Studies in experimental eosinophilia. II. Induction of peritoneal eosinophilia by the transfer of tissues and tissue extracts. Blood 16:1330.

152. Litt, M. 1962. Studies in experimental eosinophilia. IV. Determinants of eosinophil localization. J. Allergy 33:532.

153. Litt, M. 1963. Studies in experimental eosinophilia. V. Eosinophils in lymph nodes of guinea pigs following primary antigenic stimulation. Am. J. Path. 42:529.

154. Litt, M. 1964. Studies in experimental eosinophilia. VI. Uptake of immune complexes by eosinophils. J. Cell. Biol. 23:355.

155. Litt, M. 1964. Eosinophils and antigen-antibody reactions. Ann. N. Y. Acad. Sci. 116:964.

156. Litt, M. 1969. Eosinophils in lungs (Editorial). N. Engl. J. Med. 280:835.

157. Lowe, T. E. 1944. Eosinophilia in tropical disease. Med. J. Aust. 1:453.

158. Lundgren, G. 1970. *In vitro* cytotoxicity by human lymphocytes from individuals immunized against histocompatibility antigens. I. Kinetics and specificity of the reaction: influence of metabolic inhibitors and anti-lymphocyte serum. Clin. Exp. Immunol. 6:661.

159. Lutzner, M. A., and Benditt, E. P. 1963. Isolation and biochemistry of the granules of the eosinophil leukocyte of the guinea pig. J. Cell. Biol. 19:47A.

160. Mahmoud, A.A.F., Kellermeyer, R. W., and Warren, K. S. 1974. Production of monospecific rabbit antihuman eosinophil serums and demonstration of a blocking phenomenon. N. Engl. J. Med. 290:417.

161. Major, R. H., and Leger, L. H. 1939. Marked eosinophilia in Hodgkin's disease. JAMA 112:2601.

162. Makman, M. H., Nakagawa, S., and White, A. 1967. Studies on the mode of action of adrenal steroids on lymphocytes. Rec. Prog. Hormone Res. 23:195.

163. Mallory, G. K., White, P. D., and Salcedo-Salger, J. 1939. The speed of healing of myocardial infarction. A study of the pathologic anatomy of 72 cases. Am. Heart J. 18:647.

164. Mann, P. R. 1969. An electron microscope study of the relations between mast cells and eosinophil leukocytes. J. Path. 98:183.

165. Marchesi, V. T., and Florey, H. W. 1960. Electron micrographic observations on the emigration of leukocytes. Quart. J. Exp. Phys. 45:343.

166. Martin, R. R., Crowder, J. G., and White, A. 1967. Human reactions to staphylococcal antigens. A possible role of leukocyte lysosomal enzymes. J. Immunol. 99:269.

167. Martin, S. P., Chandhuri, S. H., Green, R., and McKinney, G. R. 1954. The effect of adrenal steroids on aerobic lactic acid formation in human leukocytes. J. Clin. Invest. 33:358.

168. Meincke, H. A., and Crafts, R. C. 1957. Further observations on the effect of cortisone and thyroxin on the blood picture of hypophysectomized rats. Blood 12:11.

169. Melmon, K. L., and Cline, M. J. 1967. Interaction of plasma kinins and granulocytes. Nature (Lond.) 213:90.

170. Melmon, K. L., and Cline, M. J. 1968. The interaction of kinins and the leukocyte system. Biochem. Pharmac. Suppl. 17.1:271.

171. Mesnil, M. A. 1895. Sur le mode de résistance des vertébrés inférieurs aux invasins microbiennes artificielles. Ann. de l'Inst. Pasteur 9:301.

172. Mickenberg, I. D., Root, R. K., and Wolff, S. M. 1972. Bactericidal and metabolic properties of human eosinophils. Blood 39:67.

173. Miller, F. 1966. Electron microscopic cytochemistry of leukocyte granules. *In* Proceedings ofthe Sixth International Congress of Electron Microscopy. Edited by R. Uyeda. Maruzen Co., Tokyo, p. 71.

174. Miller, F., DeHarven, E., and Palade, G. E. 1966. The structure of eosinophil leukocyte granules in rodents and man. J. Cell. Biol. 31:349.

175. Miller, T. G., and Pepper, O.H.P. 1916. Metabolic studies of angioneurotic edema. Arch. Int. Med. 18:551.

176. Morgan, J. E., and Beeson, P. B. 1971. Experimental observations on the eosinopenia induced by acute infection. Brit. J. Exp. Path. 52:214.

177. Morton, D. J., Mcran, J. F., and Stjernholm, R. L. 1969. Carbohydrate metabolism in leukocytes. X. Stimulation of eosinophils and neutrophils. J. Retic. Soc. 6:525.

178. Moschrowitz, E. 1911. Eosinophilia and anaphylaxis. N. Y. Med. J. 93:15.

179. Mowrey, F. H., and Lundberg, E. A. 1954. The clinical manifestations of essential polyangiitis (periarteritis nodosa) with emphasis on the hepatic manifestations. Ann. Intern. Med. 40:1145.

180. Muggia, F. M., Ghossein, N. A., and Wohl, H. 1973. Eosinophilia following radiation therapy. Oncology 27:118.

181. Muller, G. L. 1943. Clinical Significance of the Blood in Tuberculosis. Commonwealth Fund, New York, p. 95.

182. Müller, H. R., and Rieder, H. 1891. Ueber Vorkommen und klinische Bedeutung der eosinophilen Zellen, Ehrlich, in circulirenden Blute des Menschen. Deutsch arc. f. klin. Med. 48:96.

183. Naegli, O. 1923. Blutkrankheiten und Blutdiagnostik. Springer, Berlin.

184. Naiman, J. L., Oski, N. A., Allen, F. H., and Diamond, L. K. 1964. Hereditary eosinophilia: Report of a family and review of the literature. Am. J. Human Genetics 16:195.

185. Nattau-Larrier, L., and Parvu. M. 1909. Recherches sur le pouvoir phagocytaire des polynucleaires eosinophiles. Comptes Rend. Soc. Biol. 66:574.

186. Oberman, H. A. 1961. Idiopathic histiocytosis. A clinicopathic study of 40 cases and review of the literature on eosinophilic granuloma of bone, Hand-Schuller-Christian disease and Letterer-Siwe disease. Pediatrics 28:307.

187. Okamura, K., and Tada, T. 1971. Regulation of homocytotropic antibody formation in the rat. III. Effect of thymectomy and splenectomy. J. Immunol. 106:1019.

188. Okudaira, H., and Ishizaka, K. 1973. Reaginic antibody formation in the mouse. III. Collaboration between hapten-specific memory cells and carrier-specific helper cells for secondary anti-hapten antibody formation. J. Immunol. 111:1420.

189. Opie, E. L. 1904. An experimental study of the relation of cells with eosinophil granulation to infection with an animal parasite (*Trichinella spiralis*). Am. J. Med. Sci. 127:477.

190. Otto, P. F. 1935. Blood studies on trichuris-infested and worm-free children in Louisiana. Am. J. Trop. Med. 15:693.

191. Paplanus, S. H., and Sheldon, W. H. 1963. Acute inflammation and tissue mast cells in adrenalectomized rats with cutaneous mucormycosis. J. Exp. Med. 118:165.

192. Parish, W. E. 1970. Investigations on eosinophilia. The influence of histamine, antigen-antibody complexes containing γ1 or γ2 globulins, foreign bodies (phagocytosis) and disrupted mast cells. Brit. J. Dermatol. 82:42.

193. Parish, W. E. 1972. Eosinophilia. I. Eosinophilia in guinea pigs mediated by passive anaphylaxis and by antigen-antibody complexes containing homologous IgG1a and IgG1b. Immunology 22:1087.

194. Parish, W. E. 1972. Eosinophilia. II. Cutaneous eosinophilia in guinea pigs mediated by passive anaphylaxis with IgG1 or reagin, and antigen-antibody complexes; its relation to neutrophils and mast cells. Immunology 23:19.

195. Parish, W. E. 1972. Eosinophilia. III. The anaphylactic release from isolated human basophils of a substance that selectively attracts eosinophils. Clin. Allergy 2:381.

196. Parish, W. E., and Coombs, R.R.A. 1968. Peripheral blood eosinophilia in guinea pigs following implantation of anaphylactic guinea pig and human lung. Brit. J. Haemat. 14:425.

197. Parrush, R. S., Franco, A. E., and Schur, P. H. 1971. Rheumatoid arthritis associated with eosinophilia. Ann. Intern. Med. 75:199.

198. Pease, D. C. 1956. An electron microscopic study of red bone marrow. Blood 11:501.

199. Rackemann, F. M. 1931. Clinical Allergy. Macmillan, New York.

200. Randolph, T. G., and Rawling, F.F.A. 1945. Blood studies in allergy. III. Cellular reactions in sulphonamide sensitivity. J. Allergy 16:17.

201. Riddle, J. M., and Barnhart, M.I. 1965. The eosinophil as a source for profibrinolysin in acute inflammation. Blood 25:776.

202. Ringoen, A. R. 1938. Eosinophil leukocytes and eosinophilia. *In* Handbook of Hematology. Edited by H. Downey. Hamish Hamilton Medical Books, London, vol. 1, p. 181.

203. Roberts, A. N. 1966. Rapid uptake of tritiated antigen by mouse eosinophils. Nature (Lond.) 210:266.

204. Roberts, W. C., Liegler, D. G., and Carbone, P. P. 1969. Endomyocardial disease and eosinophilia. A clinical and pathologic spectrum. Am. J. Med. 46:28.

205. Rodnan, G. P., DiBartolomew, A. G., Medsger, T. A., Jr., and Barnes, E. L. 1975. Eosinophilic fasciitis: report of six cases of a newly recognized syndrome (Abstract). Clin. Res. 23:443A.

206. Rodriguez, M. R., and Pons, J. A. 1936. Hematological studies on schistosomiasis mansoni in Puerto Rico. J. Publ. Health & Trop. Med. 11:369.

207. Rogers, B. O., Converse, J. M., Taylor, C. A., and Campbell, R. M. 1953. Eosinophils in human skin homografting. Proc. Soc. Exp. Biol. Med. 82:523.

208. Rosenberg, E. B., Polmar, S. H., and Whalen, G. E. 1971. Increased circulating IgE in trichinosis. Ann. Intern. Med. 75:575.

209. Rosenau, W., and Moon, H. D. 1962. The inhibitory effect of hydrocortisone on lysis of homologous cells by lymphocytes *in vitro*. J. Immunol. 89:422.

210. Ross, R., and Klebanoff, S. J. 1966. The eosinophil leukocyte. J. Exp. Med. 124:653.

211. Rous, F. P. 1908. Some differential counts of the cells in the lymph of the dog: their bearing on problems of hematology. J. Exp. Med. 10:537.

212. Rytomaa, T. 1960. Organ distribution and histochemical properties of eosinophil granulocytes in the rat. Acta Path. Microbiol. Scand. 50: Suppl. 140:1.

213. Sabesin, S. M. 1963. A function of the eosinophil: Phagocytosis of antigen-antibody complexes. Proc. Soc. Exp. Biol. Med. 112:667.

214. Samter, M. 1965. Eosinophils. *In* Immunological Diseases. Edited by M. Samter and H. L. Alexander. Little, Brown & Co., Boston, p. 242.

215. Samter, M., Kofoed, M. A., and Pieper, W. 1953. A substance in the blood of anaphylactically shocked guinea pigs which can induce eosinophilia in normal animals. Blood 8:1078.

216. Schlecht, H., and Schwenker, G. 1912. Über die Beziehungen der Eosinophilie zur Anaphylaxie. Deutsch. Arch. f. klin. Med. 108:405.

217. Schleip, K. 1904. Die Homberger Trichinosisepidemic und die für Trichinosis pathognomonische Eosinophilie. Deutsch. Arch. f. klin. Med. 80:1.

218. Schriber, R. A., and Zucker-Franklin, D. 1975. Induction of blood eosinophilia by pulmonary embolization of antigen-coated particles: The relationship to cell-mediated immunity. J. Immunol. 114:1348.

219. Schwartz, H. J., Lowell, F. C., and Melby, J. C. 1968. Steroid resistance in bronchial asthma. Ann. Intern. Med. 69:493.

220. Schwartz, E. 1914. Die Lehre von der allgemeinen und örtlichen Eosinophilie. Ergebn. d. allg. Path. u. path. Anat. 17:137.

221. Scott, T.F.M., and Finland, M. 1934. Cytology of pleural effusions in pneumonias studied with supravital technique. Am. J. Med. Sci. 188:322.

222. Sears, W. G. 1932. The blood in Hodgkin's disease, with special reference to eosinophilia. Guy's Hosp. Reports 82:40.

223. Seeman, P. M., and Palade, G. E. 1967. Acid phosphatase localization in rabbit eosinophils. J. Cell. Biol. 34:745.

224. Selye, H. 1937. Studies on adaptation. Endocrinology 21:169.

225. Sewitt, S. 1955. The spleen and blood eosinophilia. J. Clin. Path. 8:42.

226. Shulman, L. E. 1975. Diffuse fasciitis with eosinophilia: A new syndrome? (Abstract). Clin. Res. 23:443A.

227. Simon, C. E. 1922. A Manual of Clinical Diagnosis. Henry Klimpton, London, p. 53.

228. Spector, W. G. 1967. Histology of allergic inflammation. Brit. Med. Bull. 23:635.

229. Speirs, R. S. 1952. The principles of eosinophil diluents. Blood 7:550.

230. Speirs, R. S. 1955. Physiological approaches to the understanding of the functions of eosinophils and basophils. Ann. N. Y. Acad. Sci. 59:706.

231. Speirs, R. S. 1970. Function of leukocytes in inflammation and immunity. *In* Regulation of Hematopoiesis. Edited by A. S. Gordon. Appleton-Century-Crofts, New York, p. 995.

232. Speirs, R. S., and Dreisbach, M. E. 1956. Quantitative studies of the cellular responses to antigen infections in normal mice. Blood 11:44.

233. Speirs, R. S., and Meyer, R. K. 1949. The effects of stress, adrenal and adrenocorticotrophic hormone on the circulating eosinophils of mice. Endocrinology 45:403.

234. Speirs, R. S., and Osada, Y. 1962. Chemotactic activity and phagocytosis of eosinophils. Proc. Soc. Exp. Biol. Med. 109:929.

235. Speirs, R. S., Speirs, E. I., and Jansen, V. 1961. A quantitative approach to the study of inflammatory cells. Proc. Soc. Exp. Biol. Med. 106:248.

236. Speirs, R. S., and Wenck, U. 1957. Effect of cortisone on the cellular response during allergic inflammation. Acta Haemat. 17:271.

237. Spink, W. W. 1934. Effects of vaccines and bacterial and parasitic infections on eosinophilia in trichinous animals. Arch. Intern. Med. 54:805.

238. Spiro, H. M. 1970. Clinical Gastroenterology. Macmillan, London, p. 176.

239. Spry, C.J.F. 1970. Eosinophil production. D.Phil. Thesis, University of Oxford.

240. Spry, C.J.F. 1971. Mechanism of eosinophilia. V. Kinetics of normal and accelerated eosinopoiesis. Cell Tissue Kinetics 4:351.

241. Spry, C.J.F. 1971. Mechanism of eosinophilia. VI. Eosinophil mobilization. Cell Tissue Kinetics 4:365.

242. Staubli, C. 1910. Die klinische Bedeutung der Eosinophilie. Ergebn. d. inn. Med. 6:192.

243. Steele, A. S., and Rack, J. H. 1965. Cellular reaction to polystyrene-protein conjugates. J. Path. Bact. 89:703.

244. Steele, R. H., and Wilhelm, D. L. 1970. The inflammatory reaction in chemical injury. III. Leukocytosis and other histological changes induced by superficial injury. Brit. J. Exp. Path. 51:265.

245. Sternon, J., Parmentieri, R., and Kenis, J. 1962. Filariose et endocarditifibroplastique. Am. Soc. Belge Med. Trop. 3:351.

246. Strauss, W. G., and Griffin, L. M. 1967. Nitrofurantoin penumonia. JAMA 199:765.

247. Sweet, L. C., Rebuck, J. W., and Noonan, S. M. 1967. The role of fibrin in allergen-induced eosinophilotaxis (Abstract). J. Allergy 39:118.

248. Swift, H. F., Miller, C. P., Jr., and Boots, R. H. 1924-25. The leucocyte curve as an index of the infection in acute rheumatic fever. J. Clin. Invest. 1:197.

249. Teir, H., Rytomaa, T., Gederberg, A., and Kiviniemi, K. 1963. Studies on the elimination of granulocytes in the intestinal tract of rats. Acta Path. Scand. 59:311.

250. Theologides, A. 1972. Unfavorable signs in patients with chronic myelocytic leukemia. Ann. Intern. Med. 76:95.

251. Thorn, G. W., Forsham, P. H., Prunty, F.T.G., and Hills, A. G. 1948. A test for adrenal cortical insufficiency: The response to pituitary adrenocorticotrophic hormone. JAMA 137:1005.

252. Torisu, M., Yoshida, T., Ward, P. A., and Cohen, S. 1973. Lymphocyte-derived eosinophil chemotactic factor. II. Studies on the mechanism of activation of the precursor substance by immune complexes. J. Immunol. 111:1450.

253. Trowell, H. C. 1960. Non-Infective Diseases in Africa. Arnold, London.

254. Vaughn, J. 1953. The function of the eosinophil leukocyte. Blood 8:1.

255. Vaughn, J. 1961. Experimental eosinophilia: Local tissue reaction to *Ascaris* extracts. J. Allergy 32:501.

256. Vercauteren, R. R. 1953. Properties of isolated granules from blood eosinophils. Enzymologia 16:1.

257. Vercauteren, R. R., and Peeters, G. 1952. On the presence of an antihistaminicum in isolated eosinophilic granulocytes. Arch. Int. Pharmacodyn. 89:10.

258. Visscher, M. B., and Halberg, F. 1955. Daily rhythms in numbers of circulating eosinophils and some related phenomena. Ann. N. Y. Acad. Sci. 59:834.

259. Wallon, D., and Browceys, J. 1957. La moelle ossense dans les éosinopenies expérimentales profundes et prolongées. Sang. 28:612.

260. Walls, R. S. 1971. Some immunological aspects of eosinophilia. D.Phil. Thesis, University of Oxford.

261. Walls, R. S., Bass, D. A., and Beeson, P. B. 1974. Mechanism of eosinophilia. X. Evidence for immunological specificity of the stimulus. Proc. Soc. Exp. Biol. Med. 145:1240.

262. Walls, R. S., Basten, A., Leuchars, E., and Davies, A.J.S. 1971. Mechanisms for eosinophilic and neutrophilic leukocytoses. Brit. Med. J. 3:157.

263. Walls, R. S., and Beeson, P. B. 1972a. Mechanism of eosinophilia. VIII. Importance of local cellular reactions in stimulating eosinophil production. Clin. Exp. Immunol. 12:111.

264. Walls, R. S., and Beeson, P. B. 1972b. Mechanism of eosinophilia. IX. Induction of eosinophilia in rats by certain forms of dextran. Proc. Soc. Exp. Biol. Med. 140:689.

265. Wámoscher, L. 1927. Über Pneumokokkeninfektionen bei verminderter individueller Resistenz. Ztschr. f. Hyg. u. Infektionskr. 107:240.

266. Ward, P. A. 1969. Chemotaxis of human eosinophils. Am. J. Path. 54:121.

267. Wasserman, S. I., Goetzl, E. J., and Austen, K. F. 1975. Inactivation of slow-reacting substance of anaphylaxis (SRS-A) by human eosinophil arylsulphatase. J. Immunol. 114:645.

268. Wasserman, S. I., Goetzl, E. J., Ellman, L., and Austen, K. F. 1974. Tumor-associated eosinophilotactic factor. N. Engl. J. Med. 290:420.

269. Weinberg, M., and Séguin, P. 1915. Recherches biologique sur l'éosinophile, deuzième partie. Propriétés phagocytaires et absorption de produits vermineux. Ann. de l'Inst. Pasteur 29:323.

270. Welsh, R. A. 1959. The genesis of the Charcot-Leyden crystal in the eosinophil leukocyte of man. Am. J. Path. 35:1091.

271. Welsh, R. A., and Geer, J. C. 1959. Phagocytosis of mast cell granules by the eosinophil leukocytes in the rat. Am. J. Path. 35:103.

272. Wetzel, B. K. 1970. The fine structure and cytochemistry of developing granulocytes, with special reference to the rabbit. *In* Regulation of Hematopoiesis. Edited by A. S. Gordon. Appleton-Century-Crofts, New York, vol. 2, p. 769.

273. Wetzel, B. K. 1970. The comparative fine structure of normal and diseased mammalian granulocytes. *In* Regulation of Hematopoiesis. Edited by A. S. Gordon. Appleton-Century-Crofts, New York, vol. 2, p. 819.

274. Williams, T. W., and Granger, G. A. 1969. Lyphocyte *in vitro* cytotoxicity: correlation of derepression with release of lymphotoxin from human lymphocytes. J. Immunol. 103:170.

275. Wilson, K. S., and Alexander, H. L. 1945. The association of periarteritis nodosa, bronchial asthma and hypereosinophilia. J. Lab. Clin. Med. 30:361, 1945.

276. Wintrobe, M. M. 1967. Clinical Hematology. Lea & Febiger, Philadelphia, p. 276.

277. Wissler, J. H., Stecher, V. J., and Sorkin, E. 1972. Biochemistry and biology of a leukotactic binary serum peptide system related to anaphylatoxin. Int. Arch. Allergy 42:722.

278. Wright, D., and Gold, E. 1946. Loeffler's syndrome associated with creeping eruption (cutaneous helminthiasis). Report of 26 cases. Arch. Intern. Med. 78:303.

279. Yamada, E., and Yamauchi, R. 1966. Some observations on the cytochemistry and morphogenesis of the granulocytes in the rat bone marrow as revealed by electron microscopy. Acta Haematol. Jap. 29:530.

280. Zappert, J. 1893. Über das Vorkommen der Eosinophilen Zellen im menschlichen Blute. Ztschr. f. klin. Med. 23:227.

281. Zolov, D. M., and Levine, B. B. 1969. Correlation of blood eosinophilia with antibody classes. Int. Arch. Allergy 35:179.

282. Zucker-Franklin, D. 1968. Electron microscopic studies of human granulocytes: Structural variations related to function. Sem. Hemat. 5:109.

283. Zucker-Franklin, D. 1971. Eosinophilia of unknown etiology: A diagnostic dilemma. Hosp. Prac. 6:119.

284. Zucker-Franklin, D. 1974. Eosinophil function and disorders. Adv. Intern. Med. 19:1.

285. Zucker-Franklin, D., Davidson, M., and Thomas, L. 1966. The interaction of mycoplasmas with mammalian cells. I. HeLa cells, neutrophils and eosinophils. J. Exp. Med. 124:521.

286. Zucker-Franklin, D., and Hirsch, J. G. 1964. Electron microscope studies of the degranulation of rabbit peritoneal leukocytes during phagocytosis. J. Exp. Med. 120:569.